Foley, S.
09/665852

-key terms

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     FILE 'CAPLUS' ENTERED AT 15:52:06 ON 01 DEC 2000
L1          596 SEA ABB=ON  PLU=ON  RECOMBIN?(S)(AAV OR (ADENOASSOC? OR
                ADENO ASSOC?)(W)VIRUS) OR RAAV
L2           93 SEA ABB=ON  PLU=ON  L1 AND (ITR OR INVERT? TERMIN?
                REPEAT)
L3           29 SEA ABB=ON  PLU=ON  L2 AND CAP
L4           29 SEA ABB=ON  PLU=ON  L3 AND REP
L5           20 SEA ABB=ON  PLU=ON  L4 AND PROMOTER
L6            5 SEA ABB=ON  PLU=ON  L4 AND (E1# OR E2#)
L7           20 SEA ABB=ON  PLU=ON  L5 OR L6

L7   ANSWER 1 OF 20  CAPLUS  COPYRIGHT 2000 ACS
ACCESSION NUMBER:         2000:666895  CAPLUS
DOCUMENT NUMBER:          133:248054
TITLE:                    Compositions and methods for helper-free
                          production of recombinant
                          adeno-associated
                          viruses
INVENTOR(S):              Gao, Guang-ping; Wilson, James M.
PATENT ASSIGNEE(S):       The Trustees of the University of Pennsylvania,
                          USA
SOURCE:                   PCT Int. Appl., 51 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   2
PATENT INFORMATION:

     PATENT NO.         KIND  DATE           APPLICATION NO.  DATE
     ---------------    ----  --------       ---------------  --------
     WO 2000055342       A1   20000921       WO 2000-US4755   20000224
         W:  AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR,
             CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
             ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
             LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU,
             SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,
             VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF,
             BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     WO 9947691          A1   19990923       WO 1999-US5870   19990318
         W:  AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU,
             CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
             IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV,
             MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG,
             SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW,
             AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE,
             DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
                          Searcher  :   Shears  308-4994
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CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: WO 1999-US5870 19990318
US 1999-404555 19990923
US 1998-78908 19980320

AB A method for producing **recombinant adeno-assocd. virus** in the absence of contaminating helper virus or wild-type virus involves culturing a mammalian host cell contg. a transgene flanked by **adeno-assocd. virus** (**AAV**) inverse terminal repeats and under the control of regulatory sequences directing expression thereof, an **AAV rep** sequence and an **AAV cap** sequence under the control of regulatory sequences directing expression thereof; and the min. adenovirus DNA required to express an **E1a** gene product, an **E1b** gene product and an **E2a** gene product, and isolating therefrom a **recombinant AAV** which expresses the transgene in the absence of contaminating helper virus or wild-type **AAV**. This method obviates a subsequent purifn. step to purify **rAAV** from contaminating virus. Also provided are various embodiments of the host cell. The invention is based on the discovery that only the adenovirus **E1** and **E2a** genes are necessary for prodn. of **recombinant AAV**. Wild-type **AAV** are not produced because the adenoviral proteins necessary for homologous **recombination** are not present.

REFERENCE COUNT: 9
REFERENCE(S): (1) Avigen Inc; WO 9717458 A 1997
(2) Cell Genesys Inc; WO 9614061 A 1996
(3) Coovert, D; CURRENT OPINION IN NEUROLOGY 1994, V7(5), P463 MEDLINE
(4) Gao, G; HUMAN GENE THERAPY 1998, V9(16), P2353 CAPLUS
(6) Shenk, T; US 5436146 A 1995 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 2000:573951 CAPLUS
DOCUMENT NUMBER: 133:173020

TITLE: Method of producing a **recombinant adeno-associated virus** using vector and helper plasmid expression constructs and therapeutic use of the virus

INVENTOR(S): Horer, Markus; Hallek, Michael
PATENT ASSIGNEE(S): Medigene A.-G., Germany

SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000047757	A1	20000817	WO 2000-EP1090	20000210
W: AU, CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
DE 19905501	A1	20000817	DE 1999-19905501	19990210

PRIORITY APPLN. INFO.: DE 1999-19905501 19990210

AB The invention relates to a method of producing a **recombinant adeno-assocd. virus** (**rAAV**). According to the inventive method, a helper construct and a vector construct are introduced into a suitable cell at different times. The helper construct contains no nucleic acid sequences, esp. except for the AAV **promoters**, to which at least one **rep** protein can substantially specifically bind. The vector construct preferably contains **ITR** sequences in flop orientation. The **recombinant adeno-assocd.** **viruses** produced according to the inventive method are esp. useful for producing a tumor cell into which addnl. nucleic acids encoding GM-CSF and B7.2 were introduced. Said tumor cell can in turn be used in the form of a medicament for the treatment of cancer.

REFERENCE COUNT: 8

REFERENCE(S):
(1) Angeletti P Ist Richerche Bio; WO 9845462 A 1998
(2) Applied Immunesciences; EP 0488528 A 1992
(3) Hallek, M; WO 9732988 A 1997
(4) Hoelscher, C; JOURNAL OF VIROLOGY 1995, V69(11), P6880 CAPLUS
(5) McCarty, D; JOURNAL OF VIROLOGY 1994, V68(8), P4988 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 20 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 2000:335582 CAPLUS

DOCUMENT NUMBER: 133:1504

TITLE: Adeno-associated virus serotype 1 nucleic acid and protein sequences and their use as gene therapy vectors in host cells

INVENTOR(S): Wilson, James M.; Xiao, Weidong

PATENT ASSIGNEE(S): The Trustees of the University of Pennsylvania, USA

SOURCE: PCT Int. Appl., 108 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000028061	A2	20000518	WO 1999-US25694	19991102
WO 2000028061	A3	20000803		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1998-107114 19981105

AB The nucleic acid sequences of adeno-assocd. virus (AAV) serotype 1 are provided, as are vectors and host cells contg. these sequences and functional fragments thereof. The entire AAV-1 genome is 4718 nucleotides in length, within the range of other known serotypes. Amon particularable desirable AAV-1 fragments are the **inverted terminal repeat** sequences (**ITRs**), **rep** genes, and capsid genes. Also provided are methods of delivering genes via AAV-1 derived vectors. Cassettes may contain the **AAV**-1 **ITRs** of the invention flanking a selected transgene, or the **rep** and/or **cap** proteins for use in producing **recombinant** virus. Exemplary transducing vectors based on AAV-1 capsid proteins and conting. genes encoding human .alpha.1-antitrypsin or murine erythropoietin under control of a cytomegalovirus-enhanced .beta.-actin **promoter** are tested both in vivo and in vitro.

L7 ANSWER 4 OF 20 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 2000:321571 CAPLUS

DOCUMENT NUMBER: 132:304277

TITLE: A novel **recombinant adeno-associated virus** vector packaging system with HSV-1 amplicon as helper virus

INVENTOR(S): Shu, Yuelong; Yan, Ziying; Hou, Yunde

PATENT ASSIGNEE(S): Inst. of Viroloty, China Prevention Medical Academy, Peop. Rep. China

SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 9 pp.
CODEN: CNXXEV

DOCUMENT TYPE: Patent

LANGUAGE: Chinese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1213699	A	19990414	CN 1997-116981	19971008

AB A novel simple and scaleable packaging system for producing **recombinant adeno-assocd. virus** (**rAAV**) vector with HSV-1 amplicon as helper virus is described. The chimeric HSV-1 and AAV vector pHSV-AAV(+/-) expressing genes for AAV-2 replication and capsid protein from their native **promoters** is used as helper virus for **rAAV** replicating and packaging. The HSV-1 amplicon is selected from two kinds of infectious HSV-1 virions, a replicating-defective HSV-1 amplicon pseudovirus harboring multi-copies of AAV-2 **rep** and **cap** gene or a temp.-sensitive HSV-1 mutant strain ts-KOS. The AAV packaging signal is provided by plasmid pBDZ(+) or pBDZ(-)which contains a replication origin oriP from EBV (HSV-4), EBNA-1 gene, hyg (or hph, for hygromycin B resistance gene) as selection marker, AAV-2 **ITR**, CMV early **promoter**, ampr gene and Escherichia coli vector sequence. Methods for prepg. high-titer **rAAV** by transfecting Vero cells stably transfected with plasmid pBDZ(+) or pBDZ(-) are provided.

L7 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:795943 CAPLUS
DOCUMENT NUMBER: 132:45813
TITLE: Generation of **recombinant adeno-associated virus** vectors without formation of wild-type virus
INVENTOR(S): Srivastava, Arun; Wang, Xu-Shan; Ponnazhagan, Selvarangan
PATENT ASSIGNEE(S): Advanced Research and Technology Institute, USA
SOURCE: PCT Int. Appl., 100 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9964569	A1	19991216	WO 1999-US13070	19990609

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE,

DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9945587 A1 19991230 AU 1999-45587 19990609

PRIORITY APPLN. INFO.: US 1998-88714 19980610
WO 1999-US13070 19990609

AB A plasmid co-transfection system for the generation of **recombinant adeno-assocd. virus** 2 for use as a gene delivery virus that minimizes the generation of wild-type virus by preventing homologous **recombination** is described. Recombination is dependent upon 10 nucleotides of the viral D-sequence and helper vectors lacking sequence homol. in the D-sequence and helper plasmids lacking adenovirus **inverted terminal repeats**. Methods and compns. for the use of **recombinant AAV** plasmids and helper vectors lacking homol. in the D-sequence, and helper plasmids lacking the adenovirus **ITRs** for use in gene therapy are described. Mapping of recombination events leading to the generation of wild-type virus found most of them clustering in the 10 distal nucleotides of the D-sequence and also involved the **inverted terminals repeats** of the adenovirus 5 helper. Deletion of selected sequences gradually lowered the titer of wild-type virus to <0.1% of total virus.

REFERENCE COUNT: 6

REFERENCE(S):

(1) Qing; Journal of Virology 1998, V72(2), P1593 CAPLUS
(2) Wang; Journal of Molecular Biology 1995, V250, P573 CAPLUS
(3) Wang; Journal of Virology 1996, V70(3), P1668 CAPLUS
(4) Wang; Journal of Virology 1997, V71(2), P1140 CAPLUS
(5) Wang; Journal of Virology 1997, V71(4), P3077 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 6 OF 20 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1999:614159 CAPLUS

DOCUMENT NUMBER: 131:224468

TITLE: Cells and methods for helper-free production of **recombinant adeno-associated viruses**

INVENTOR(S): Gao, Guang-Ping; Wilson, James M.

PATENT ASSIGNEE(S): Trustees of the University of Pennsylvania, USA

SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9947691	A1	19990923	WO 1999-US5870	19990318
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9930973	A1	19991011	AU 1999-30973	19990318
WO 2000055342	A1	20000921	WO 2000-US4755	20000224
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
PRIORITY APPLN. INFO.:			US 1998-78908	19980320
			WO 1999-US5870	19990318
			US 1999-404555	19990923

AB A method for producing **recombinant adeno-assocd. virus** in the absence of contaminating helper virus or wild-type virus involves culturing a mammalian host cell contg. a transgene flanked by **adeno-assocd. virus** (**AAV**) inverse terminal repeats and under the control of regulatory sequences directing expression thereof, an **AAV rep** sequence and an **AAV cap** sequence under the control of regulatory sequences directing expression thereof; and the min. adenovirus DNA required to express an **E1a** gene product, an **E1b** gene product and an **E2a** gene product, and isolating therefrom a **recombinant AAV** which expresses the transgene in the absence of contaminating helper virus or wildtype **AAV**. This method obviates a subsequent purifn. step to purify **rAAV** from contaminating virus. Also provided are various embodiments of the host cell. The invention is based on the discovery that only the adenovirus **E1** and **E2a** genes are necessary for prodn. of **recombinant AAV** . Wild-type **AAV** are not produced because the adenoviral proteins necessary for homologous **recombination** are not present.

REFERENCE COUNT: 9

REFERENCE(S):
(1) Avigen Inc; WO 9717458 A 1997
(2) Cell Genesys Inc; WO 9614061 A 1996
(3) Coovert, D; Current Opinion in Neurology 1994, V7(5), P463 MEDLINE
(4) Gao, G; Human Gene Therapy 1998, V9(16), P2353 CAPLUS
(6) Shenk, T; US 5436146 A 1995 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 7 OF 20 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:529279 CAPLUS
DOCUMENT NUMBER: 131:140502
TITLE: Helper adenovirus free **recombinant adeno-associated virus** (**rAAV**) vector production in mammalian cells
INVENTOR(S): Wadsworth, Samuel C.
PATENT ASSIGNEE(S): Genzyme Corporation, USA
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9941399	A1	19990819	WO 1999-US3482	19990217
W: AU, CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9926859	A1	19990830	AU 1999-26859	19990217
PRIORITY APPLN. INFO.:			US 1998-74762	19980217
			WO 1999-US3482	19990217

AB The novel systems for the high level prodn. of purified **recombinant adeno-assocd. virus** (**rAAV**) vector stocks comprising producer cell lines and helper adenoviruses are described. These systems provide high level prodn. of purified **rAAV** vector stocks that are not contaminated by helper viruses or have very minimal contamination with helper virus. The helper virus is preferably a temp.-sensitive mutant of a human adenovirus which is capable of entering the producer cell line, but cannot generate a productive infection. The producer cell line is preferably non-human and comprises genes encoding the **rAAV** vector (and transgene), as well as helper adenovirus gene for CAR receptor stably integrated into its genome. Also provided a novel adenovirus/**rAAV** hybrid vector which can be used to produce an **rAAV** vector stock. The hybrid vector contains all essential adenovirus coding sequences

and also an **rAAV** genome comprising a transgene operably linked to expression control elements and flanked by the AAV **ITR** sequences.

REFERENCE COUNT: 4
REFERENCE(S):
(1) Dedieu, J; WO 9622378 A 1996
(2) Ferrari, F; NATURE MEDICINE 1997, V3(11), P1295 CAPLUS
(3) Wadsworth, S; WO 9709441 A 1997
(4) Wilson, J; WO 9613598 A 1996

L7 ANSWER 8 OF 20 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:286101 CAPLUS
DOCUMENT NUMBER: 130:292450
TITLE: Preparation of the gene delivery adeno-associated virus vectors using herpes virus DISC as a helper virus and their uses for gene therapy
INVENTOR(S): Zhang, Xiaoliu
PATENT ASSIGNEE(S): Cantab Pharmaceuticals Research Limited, UK
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9920778	A1	19990429	WO 1998-GB3114	19981019
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9894528	A1	19990510	AU 1998-94528	19981019
EP 1023452	A1	20000802	EP 1998-947691	19981019
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRIORITY APPLN. INFO.:			GB 1997-21909	19971017
			WO 1998-GB3114	19981019

AB Prepn. of adeno-assocd. virus (AAV) gene delivery vectors using herpes virus DISC (disabled infectious single cycle) particles as a helper virus as well as delivery of a coagulation factor IX gene to target cells is disclosed. The method uses herpesvirus replication functions (oriS and a packaging signal) to replicate DNA carrying a

foreign gene that is flanked by adeno assocd. virus **inverted terminal repeats** and carrying the viral **rep** and **cap** genes. The vector is used to infect a producer cell that uses the herpesvirus replication function to replicate and package the AAV. The virus is then used to infect target host cells, with expression of the therapeutic gene. Chosen DNA for delivery to and expression in target cells can comprise DNA encoding one or more heterologous genes, e.g. genes encoding antigens or cytokines or other immunostimulatory or other immunomodulatory proteins.

REFERENCE COUNT: 6

REFERENCE(S):
(1) Bilbao, G; FASEB Journal 1997, V11, P624 CAPLUS
(2) Inglis, S; WO 9421807 A 1994
(3) Johnston, K; Human Gene Therapy 1997, V8(3), P359 CAPLUS
(4) Lebkowski, J; US 5354678 A 1994 CAPLUS
(5) UAB Research Foundation; WO 9506743 A 1995
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 9 OF 20 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:244775 CAPLUS
DOCUMENT NUMBER: 130:292438
TITLE: Chimeric **AAV**/B19 parvovirus-based **recombinant** vector system specifically targeting the erythroid lineage
INVENTOR(S): Srivastava, Arun; Ponnazhagan, Selvarangan
PATENT ASSIGNEE(S): Advanced Research and Technology Institute, USA
SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9918227	A1	19990415	WO 1998-US21202	19981008
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9912696	A1	19990427	AU 1999-12696	19981008
EP 1027451	A1	20000816	EP 1998-956097	19981008

Searcher : Shears 308-4994

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PRIORITY APPLN. INFO.: US 1997-61364 19971008
WO 1998-US21202 19981008

AB The present invention relates to the engineering, propagation and use of chimeric parvovirus vectors using sequences from adeno-assocd. virus (AAV) and B19 virus, which may be used to deliver genes to various target cells, including those of erythroid lineage. The system exploits the unique features of AAV and B19 such that it does not suffer from toxicity, oncogenicity, or immunogenicity concerns. Heterologous DNA sequences are cloned withing the **inverted terminal repeats** (**ITR**) of AAV, without the presence of any AAV structural genes, and subsequently packaged inside the capsid structure of B19. Such a chimeric vector is achieved by creating a helper plasmid consisting of the **rep** gene of AAV, and the **cap** gene of B19. High titers of the vector may be generated, facilitating in vivo therapy. It is designed to specifically target primitive progenitor and differentiated cells of erythroid lineage, and can achieve stable integration and expression of transduced genes.

REFERENCE COUNT: 11

REFERENCE(S):

(4) Ponnazhagan, S; Blood, Meeting Info: 39th Annual Meeting of the American Society of Hematology 1997 CAPLUS

(5) Ponnazhagan, S; J Virology 1998, V72(6), P5224 CAPLUS

(8) Shimada, T; US 5508186 A 1996 CAPLUS

(9) Srivastava, C; Proceedings of the National Academy of Sciences of USA 1989, V86(20), P8078 CAPLUS

(11) Wong, S; J Virology 1994, V68(7), P4690 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 10 OF 20 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1999:223068 CAPLUS

DOCUMENT NUMBER: 130:247865

TITLE: Manufacture of **recombinant adeno-associated viruses** in high titer using producer cells carrying integrated **rep** and **cap** genes

INVENTOR(S): Wilson, James M.; Gao, Guang-Ping

PATENT ASSIGNEE(S): The Trustees of the University of Pennsylvania, USA

SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9915685	A1	19990401	WO 1998-US19463	19980918
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9893970	A1	19990412	AU 1998-93970	19980918
EP 1015619	A1	20000705	EP 1998-947114	19980918
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: US 1997-59340 19970919
WO 1998-US19463 19980918

AB Methods for efficient prodn. of **recombinant adeno -assocd. virus** (**AAV**) using a host cell carrying the **AAV rep** and **cap** genes stably integrated into the cell's chromosomes are described. The integrated **rep** and **cap** genes are under the control of **promoters** that are induced by a specific stimulus such as infection of the cell with a helper virus, or introduction of a helper gene or helper gene product. Preferably, the **rep** and **cap** genes are integrated in tandem repeat arrays under control of the AAv p5 **promoter**. Cells in which the genes have been induced are then superinfected with a virus or plasmid vector contg. adenovirus cis-elements necessary for replication and virion encapsidation, AAV sequences comprising the 5' and 3' **ITRs**, and a selected gene operatively linked to regulatory sequences directing its expression, which is flanked by the above-mentioned AAV sequences. The vector to be packaged does not carry the **rep** and **cap** genes. The resulting AAV is essentially free of replication competent virus and yields of virus of .gtoreq.103 per cell are obtained. A novel B50 producer cell line is described. AAV carrying a monkey erythropoietin gene constructed using this method were injected into immune-deficient or immune-competent mice. Virus manufd. with B50 cells was more infective than that manufd. with the prior art 293 cell system. The mice had .apprx.4-fold higher levels of erythropoietin and a significantly higher hematocrit than control cells. Cells manufd.

REFERENCE COUNT: 8
REFERENCE(S): (1) Allen, J; WO 9617947 A 1996
Searcher : Shears 308-4994

(3) Clark, K; Gene Therapy 1996, V3, P1124 CAPLUS
(4) Clark, K; Human Gene Therapy 1995, V6(10), P1329 CAPLUS
(5) Flotte, T; Gene Therapy 1995, V2(1), P29 CAPLUS
(7) Tamayose, K; Human Gene Therapy 1996, V7(4), P507 MEDLINE
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 11 OF 20 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:109391 CAPLUS
DOCUMENT NUMBER: 130:163981
TITLE: Adeno-associated virus vector replication and encapsidation system based on novel **inverted terminal repeat** sequence
INVENTOR(S): Samulski, Richard Jude; Xiao, Xiao
PATENT ASSIGNEE(S): The University of Pittsburgh, USA
SOURCE: U.S., 27 pp., Cont.-in-part of U.S. Ser. No. 989,841.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5869305	A	19990209	US 1995-440738	19950515
US 5478745	A	19951226	US 1992-989841	19921204
US 6057152	A	20000502	US 1995-471914	19950606
CA 2221292	AA	19961121	CA 1996-2221292	19960514
WO 9636364	A1	19961121	WO 1996-US6786	19960514
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9658577	A1	19961129	AU 1996-58577	19960514
AU 699973	B2	19981217		
EP 828519	A1	19980318	EP 1996-920191	19960514
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 11506318	T2	19990608	JP 1996-534946	19960514
PRIORITY APPLN. INFO.:			US 1992-989841	19921204
			US 1995-440738	19950515
			WO 1996-US6786	19960514

AB Claimed is a system for replication and encapsidation of **recombinant** DNA fragments into virus particles comprised of adenovirus assocd. viral (**AAV**) capsid proteins, including

a novel 165 bp DNA fragment contg. **AAV inverted terminal repeat** (**ITR**) sequences capable of directing replication and encapsidation. The invention provides a means of obtaining recombinant viral stocks that may be used to treat patients suffering from genetic diseases.

REFERENCE COUNT: 12

REFERENCE(S):
(3) Cheung, A; J Virol 1980, V33, P739 CAPLUS
(4) Kotin, R; Proc Natl Acad Sci USA 1990, V87, P2211 CAPLUS
(6) Muzyczka; US 5139941 1992 CAPLUS
(7) Muzyczka, N; Current Topics in Microbiol & Immunol 1992, V158, P97 CAPLUS
(8) Philip, R; Mol Cell Biol 1994, V14, P2411 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 12 OF 20 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1999:63217 CAPLUS
DOCUMENT NUMBER: 130:262913

TITLE: Cloning and characterization of adeno-associated virus type 5

AUTHOR(S): Chiorini, John A.; Kim, Frank; Yang, Linda; Kotin, Robert M.
CORPORATE SOURCE: Molecular Hematology Branch, National Heart, Lung and Blood Institute, Bethesda, MD, 20892, USA

SOURCE: J. Virol. (1999), 73(2), 1309-1319
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Adeno-assocd. virus type 5 (AAV5) is distinct from other dependovirus serotypes based on DNA hybridization and serol. data. To better understand the biol. of AAV5, we have cloned and sequenced its genome and generated recombinant AAV5 particles. The single-stranded DNA genome is similar in length and genetic organization to that of AAV2. The **rep** gene of AAV5 is 67% homologous to AAV2, with the majority of the changes occurring in the carboxyl and amino termini. This homol. is much less than that obsd. with other reported AAV serotypes. The **inverted terminal repeats** (**ITRs**) are also unique compared to those of the other AAV serotypes. While the characteristic AAV hairpin structure and the **Rep** DNA binding site are retained, the consensus terminal resoln. site is absent. These differences in the **Rep** proteins and the **ITRs** result in a lack of cross-complementation between AAV2 and AAV5 as measured by the prodn. of **recombinant AAV** particles. Alignment of the **cap** open reading frame with that of the other AAV serotypes identifies both conserved

and variable regions which could affect tissue tropism and particle stability. Comparison of transduction efficiencies in a variety of cells lines and a lack of inhibition by sol. heparin indicate that AAV5 may utilize a distinct mechanism of uptake compared to AAV2.

REFERENCE COUNT: 56

REFERENCE(S):
(4) Chapman, M; Virology 1993, V194, P491 CAPLUS
(5) Chejanovsky, N; Virology 1989, V173, P120 CAPLUS
(6) Chejanovsky, N; Virology 1989, V171, P239 CAPLUS
(7) Chiorini, J; Hum Gene Ther 1995, V6, P1531 CAPLUS
(8) Chiorini, J; J Virol 1994, V68, P7448 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 13 OF 20 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:605015 CAPLUS
DOCUMENT NUMBER: 129:198915
TITLE: Expression vector for the permanent expression of foreign DNA
INVENTOR(S): Grummt, Ingrid; Grummt, Friedrich
PATENT ASSIGNEE(S): Deutsches Krebsforschungszentrum Stiftung des Offentlichen Rechts, Germany
SOURCE: PCT Int. Appl., 10 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9837209	A2	19980827	WO 1998-DE539	19980224
WO 9837209	A3	19981126		
W: CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
DE 19707273	C1	19980924	DE 1997-19707273	19970224
EP 968296	A2	20000105	EP 1998-914811	19980224
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, NL, SE				

PRIORITY APPLN. INFO.: DE 1997-19707273 19970224
WO 1998-DE539 19980224

AB The present invention relates to an expression vector for expressing foreign DNA. Said DNA at its 3' end has a sequence which prevents the replication of the expression vector from occurring in the opposite direction to the transcription of said expression vector. The invention also relates to a prepn. contg. such an expression vector and to the use of both in the permanent expression of foreign DNA in cells. Thus, expression vector pAAV-ADA, comprising

adeno-assocd. virus 5'- and 3'-**ITRs**, mouse metallothionein **promoter**, human adenosine deaminase cDNA, SV40 poly A sequence, and a replication fork barrier, was prepd. COS cells infected with adenovirus and expressing AAV **rep** and **cap** genes were used to prep. virus particles. Infection of cells with these virus particles led to permanent expression of the ADA gene.

L7 ANSWER 14 OF 20 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:527447 CAPLUS
DOCUMENT NUMBER: 129:145616
TITLE: A conditional replication and expression system and its use for packaging of adeno-associated virus vectors
INVENTOR(S): Einerhand, Markus Peter Wilhelmus; Valerio, Domenico
PATENT ASSIGNEE(S): Introgene B.V., Neth.
SOURCE: PCT Int. Appl., 92 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9832870	A1	19980730	WO 1998-NL61	19980129
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9858844	A1	19980818	AU 1998-58844	19980129
EP 979297	A1	20000216	EP 1998-902284	19980129
R: BE, CH, DE, ES, FR, GB, IT, LI, LU, NL				
PRIORITY APPLN. INFO.:			EP 1997-200245	19970129
			WO 1998-N	

L61 19980129
AB The present invention relates to the utilization of conditionally replicating recombinant nucleic acid mols. rescued from the integrated state for the expression of foreign proteins. The usefulness of the system is illustrated with a conditionally replicating **recombinant** nucleic acid mol. encoding **adeno-assocd. virus** (**AAV**) capsid proteins. The present invention also relates to methods

employing said conditionally replicating **recombinant** nucleic acid mols. for the packaging of **recombinant** **AAV** nucleic acid mols. into **AAV** capsids. The present invention also relates to packaging cell lines for **recombinant** **AAV**, expressing both the **AAV** **rep** and **cap**-genes. Thus, cell line CARE.1, for packaging of adeno-assocd. virus vectors was created. This cell line was prepd. from a HeLa cell which constitutively expresses the tet repressor-VP16 fusion (transactivator tA). Also integrated into the genome of this cell line was a tetO-**promoter** P5-**rep-cap** construct and a **cap** gene flanked by AAV **ITRs**. Expression of the **rep** proteins is repressed by doxycycline; expression of the **rep** proteins results when doxyclycline is removed from the system. **Recombinant** adeno-assocd. vectors can be packaged with CARE.1 by removing doxycycline and transfecting with adenovirus and with an **AAV** expression construct consisting of a gene flanked by **AAV** **ITRs**.

L7 ANSWER 15 OF 20 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:176034 CAPLUS
DOCUMENT NUMBER: 128:214185
TITLE: Use of the cre-loxP system to control expression of genes in the manufacture of adenovirus vectors for gene therapy
INVENTOR(S): Wilson, James M.; Phaneuf, Daniel
PATENT ASSIGNEE(S): Trustees of the University of Pennsylvania, USA; Wilson, James M.; Phaneuf, Daniel
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9810086	A1	19980312	WO 1997-US15691	19970904
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9741830	A1	19980326	AU 1997-41830	19970904
AU 722375	B2	20000803		

Searcher : Shears 308-4994

EP 950111 A1 19991020 EP 1997-939821 19970904
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
PRIORITY APPLN. INFO.: US 1996-25323 19960906
WO 1997-US15691 19970904

AB A method for the manuf. of adeno-assocd. virus carrying a foreign gene in which the cre-loxP system is used to regulate expression of the **rep/cap** genes is described. Regulated expression of these genes allows efficient packaging of a gene flanked by adeno-assocd. virus **inverted terminal repeats** without a build up of toxic levels of the **rep** gene product. The method uses three vectors. A first vector is an expression vector for the cre gene, the second is an expression vector for the **rep/cap** genes in which the **promoter** is sepd. from the coding region by an insert flanked by loxP sites and **rep/cap**, and a third vector contains a minigene contg. a transgene and regulatory sequences flanked by AAV **ITRs**. The third vector contains an expression cassette for the therapeutic gene flanked by AAV **inverted terminal repeats**. The host cell stably or inducibly expresses the cre gene and two vectors carrying the other elements of the system are introduced into the host cell.

L7 ANSWER 16 OF 20 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:169418 CAPLUS
DOCUMENT NUMBER: 128:227084
TITLE: Methods and compositions for liver-specific delivery of therapeutic molecules using **recombinant adeno-associated virus** vectors
INVENTOR(S): Srivastava, Aron; Ponnazhagan, Selvarangan; Chloemer, Robert H.; Wang, Xu-Shan; Yoder, Mervin C.; Zhou, Shang-Zhen; Escobedo, Jaime; Dwarki, Varavani
PATENT ASSIGNEE(S): Chiron Corporation, USA; Indiana University
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9809524	A1	19980312	WO 1997-US15453	19970902

W: CA, JP
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

EP 933997 A1 19990811 EP 1997-940762 19970902
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
PRIORITY APPLN. INFO.: US 1996-25616 19960906
US 1996-25649 19960911
WO 1997-US15453 19970902

AB Provided are methods for selectively expressing therapeutic mols., such as secretory proteins, antisense mols. and ribozymes, in the liver. The methods find use in treating hepatic diseases or conditions. The methods also find use in treating any disease or condition in which systemic administration of the therapeutic substance, for example, a secretory protein, is desired. The methods involve administering to a mammalian patient having a need for liver expression of a therapeutic mol. an AAV vector contg. a therapeutically effective amt. of the therapeutic mol. Also provided are novel vectors employable in these methods. Expts. revealed that, following i.v. injection of AAV vectors into mice, the AAV genomes were found predominantly in the liver. The heterologous genes carried by these vectors (chimeric cytomegalovirus **promoter**-lacZ or .beta.-globin **promoter**-globin genes) were expressed in the liver. Cotransfection of adenovirus 2-infected 293 cells with the AAV vectors and helper plasmid contg. **cap** and **rep** genes resulted in prodn. of 0.1-10% wild-type AAV. Replacement of the last 10 nucleotides of the **ITR** D sequence with unrelated nucleotides reduced this illegitimate recombination was reduced. Four **recombinant AAV** vectors (pD-5, pD-10, pD-15 and pD-20) with such modified **ITR** regions were prepd.

L7 ANSWER 17 OF 20 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:262359 CAPLUS
DOCUMENT NUMBER: 126:234449
TITLE: **Adeno-associated virus recombinant** vectors comprising **inverted terminal repeat** and gene of interest, packaging cell lines, and gene therapy
INVENTOR(S): Wadsworth, Samuel C.; Vincent, Karen; Piraino, Susan; Kyostio, Sirkka
PATENT ASSIGNEE(S): Genzyme Corporation, USA; Wadsworth, Samuel C.; Vincent, Karen; Piraino, Susan; Kyostio, Sirkka
SOURCE: PCT Int. Appl., 84 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9709441	A2	19970313	WO 1996-US14423	19960906
W: AU, CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2230758	AA	19970313	CA 1996-2230758	19960906
AU 9669173	A1	19970327	AU 1996-69173	19960906
AU 715543	B2	20000203		
EP 850313	A2	19980701	EP 1996-929952	19960906
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 11514853	T2	19991221	JP 1996-511437	19960906
PRIORITY APPLN. INFO.:			US 1995-3470	19950908
			WO 1996-US14423	19960906

AB The present invention is directed to methods for generating high titer, contaminant free, **recombinant adeno-assocd. virus** (**AAV**) vectors, methods and genetic constructs for producing **AAV recombinant** vectors conveniently and in large quantities, methods for the delivery of all essential viral proteins required in trans for high yields of **recombinant AAV**, **recombinant AAV** vectors for use in gene therapy, novel packaging cell lines which obviate the need for cotransfection of vector and helper plasmids, helper plasmids and vector plasmid backbone constructs, and a reporter assay for detg. **AAV** vector yield. Further provided are **recombinant AAV** vectors in a pharmaceutically acceptable carrier, methods of delivering a transgene of interest to a cell, compns. and methods for delivering a DNA sequence encoding a desired polypeptide to a cell, and transgenic non-human mammals that express a human chromosome 19 **AAV** integration locus.

L7 ANSWER 18 OF 20 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:48854 CAPLUS
DOCUMENT NUMBER: 126:65388
TITLE: Recombinant viral vector system
INVENTOR(S): Samulski, Richard J.; Xiao, Xiao
PATENT ASSIGNEE(S): Samulski, Richard, J., USA; Xiao, Xiao
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9636364	A1	19961121	WO 1996-US6786	19960514

Searcher : Shears 308-4994

W: AU, CA, JP
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

US 5869305	A	19990209	US 1995-440738	19950515
AU 9658577	A1	19961129	AU 1996-58577	19960514
AU 699973	B2	19981217		
EP 828519	A1	19980318	EP 1996-920191	19960514
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 11506318	T2	19990608	JP 1996-534946	19960514
PRIORITY APPLN. INFO.:			US 1995-440738	19950515
			US 1992-989841	19921204
			WO 1996-US6786	19960514

AB The present invention relates to a system for replication and encapsidation of **recombinant** DNA fragments into virus particles comprised of adeno-assocd. viral (**AAV**) capsid proteins; said system uses a 165-basepair fragment of DNA which contains **AAV inverted terminal repeat** sequences and which is used to engineer expression vectors useful for gene therapy. The invention provides a means of obtaining recombinant viral stocks that may be used to treat patients suffering from genetic diseases.

L7 ANSWER 19 OF 20 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:106583 CAPLUS
DOCUMENT NUMBER: 124:137857
TITLE: **Recombinant adeno-associated virus** vectors encoding immunodeficiency virus protein and their clinical use
INVENTOR(S): Johnson, Philip R.
PATENT ASSIGNEE(S): Children's Hospital, Inc., USA
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9534670	A2	19951221	WO 1995-US7178	19950606
WO 9534670	A3	19960613		
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5658785	A	19970819	US 1994-254358	19940606
CA 2192215	AA	19951221	CA 1995-2192215	19950606
AU 9531243	A1	19960105	AU 1995-31243	19950606

Searcher : Shears 308-4994

AU 710804	B2	19990930		
EP 764213	A1	19970326	EP 1995-927113	19950606
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 10504185	T2	19980428	JP 1995-502305	19950606
US 5786211	A	19980728	US 1995-475391	19950607
US 5858775	A	19990112	US 1996-709609	19960910
PRIORITY APPLN. INFO.:			US 1994-254358	19940606
			WO 1995-US7178	19950606

AB The present invention provides adeno-assocd. virus (AAV) materials and methods which are useful for DNA delivery to cells. More particularly, the invention provides **recombinant AAV** (**rAAV**) genomes, comprising **adeno-assocd. virus inverted terminal repeats** flanking DNA sequences encoding an immunodeficiency virus protein operably linked to **promoter** and polyadenylation sequences, methods for packaging **rAAV** genomes, stable host cell lines producing **rAAV** and methods for delivering genes of interest to cells utilizing the **rAAV** . Particularly disclosed are **rAAV** useful in generating immunity to human immunodeficiency virus-1 and in therapeutic gene delivery for treatment of neurol. disorders.

L7 ANSWER 20 OF 20 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:748965 CAPLUS
DOCUMENT NUMBER: 123:135121
TITLE: A pair of adeno-associated virus vector systems for the generation of high titers infectious adeno-associated virus particles carrying a foreign gene
INVENTOR(S): Kotin, Robert; Chiorini, John A.; Safer, Brian; Urcelay, Elena
PATENT ASSIGNEE(S): United States Dept. of Health and Human Services, USA; Genetic Therapy, Inc.
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9514771	A1	19950601	WO 1994-US13516	19941121
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5693531	A	19971202	US 1993-157740	19931124
CA 2176600	AA	19950601	CA 1994-2176600	19941121

Searcher : Shears 308-4994

EP 736092 A1 19961009 EP 1995-904118 19941121
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
JP 09505480 T2 19970603 JP 1994-515208 19941121
PRIORITY APPLN. INFO.: US 1993-157740 19931124
WO 1994-US13516 19941121

AB A pair of adeno-assocd. virus (AAV) vector-based vectors that are used to generate high titers of virus carrying the foreign gene are described for use in genetic engineering of animal cells and in gene therapy (no data). The first vector carries the 5'- and 3'- **inverted terminal repeats** of AAV and the foreign gene. The second vector includes an inducible origin of replication, such as from SV40, that is capable of being induced or activated by an agent, such as the SV40 T-antigen. This vector also includes DNA sequences encoding the adeno-assocd. virus **rep** and **cap** proteins and an inducible expression cassette for the inducer of replication. When induced by an agent, the second vector may replicate to a high copy no., and thereby increased nos. of infectious adeno-assocd. viral particles may be generated.

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 15:56:04 ON 01 DEC 2000)
L8 20 S L7
L9 20 DUP REM L8 (0 DUPLICATES REMOVED)

L9 ANSWER 1 OF 20 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-647078 [62] WPIDS
CROSS REFERENCE: 1999-562121 [47]
DOC. NO. CPI: C2000-195682
TITLE: Adenovirus/**AAV** hybrid virus comprising a **recombinant** adeno associated viral (**rAAV**) vector and nucleic acid sequences encoding adenovirus **E1a** and **E1b** , useful for somatic gene therapy.
DERWENT CLASS: B04 D16
INVENTOR(S): GAO, G; WILSON, J M
PATENT ASSIGNEE(S): (UYPE-N) UNIV PENNSYLVANIA
COUNTRY COUNT: 90
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000055342	A1	20000921	(200062)*	EN	51

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000055342 A1		WO 2000-US4755	20000224

PRIORITY APPLN. INFO: US 1999-404555 19990923; WO 1999-US5870 19990318

AN 2000-647078 [62] WPIDS

CR 1999-562121 [47]

AB WO 200055342 A UPAB: 20001130

NOVELTY - An adenovirus/**AAV** hybrid virus comprising a **recombinant** adeno associated viral (**rAAV**) vector and nucleic acid sequences encoding adenovirus **E1a** and **E1b** under the control of regulatory sequences, where the hybrid virus contains sufficient adenoviral sequences to permit replication in a selected host cell, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an adenovirus/AAV hybrid virus comprising:

(a) adenovirus 5' cis-elements necessary for replication and packaging;

(b) a deletion of adenoviral sequences in the native adenoviral **E1a** and **E1b** region;

(c) an **rAAV** vector;

(d) a deletion of adenoviral sequences from the E3 region;

(e) nucleic acid sequences encoding adenovirus **E1a** and adenovirus **E1b** under the control of regulatory sequences directing expression of the **E1a** and **E1b** gene products, where the **E1a** and **E1b** nucleic acid sequences are located in the site of the E3 region; and

(f) adenovirus 3' cis-elements necessary for replication and packaging;

(2) a method for producing **rAAV** by culturing a host cell comprising:

(a) an AAV **rep** sequence and an AAV **cap** sequence under the control of regulatory sequences directing expression; and

(b) an adenovirus/**AAV** hybrid virus comprising a **recombinant** adeno associated viral (**rAAV**) vector and nucleic acid sequences encoding adenovirus **E1a** and adenovirus **E1b** under the control of regulatory sequences directing expression of the **E1a** and **E1b** gene products, where the hybrid virus contains sufficient adenoviral sequences to permit replication of the hybrid virus in a selected host cell;

(3) **recombinant AAV** produced according to

the method of (2);

(4) a method for producing **rAAV** in the absence of contaminating helper virus or wild-type virus by culturing a host cell comprising:

(a) an AAV **rep** sequence and an AAV **cap** sequence under the control of regulatory sequences directing expression; and

(b) an adenovirus/**AAV** hybrid virus comprising a **recombinant** adeno associated viral (**rAAV**) vector and nucleic acid sequences encoding adenovirus **E1a** and adenovirus **E1b** under control of regulatory sequences directing expression of the **E1a** and **E1b** gene products, where the hybrid virus contains sufficient adenoviral sequences to permit replication of the hybrid virus in a selected host cell, where the host cell is cultured under conditions which control replication of the hybrid virus, thus enhancing yield of **rAAV**; and

(5) a mammalian host cell containing an adenovirus/AAV hybrid virus as above.

ACTIVITY - None given.

MECHANISM OF ACTION - Gene therapy.

USE - The adenovirus/AAV hybrid virus can be used to transform a host cell, and in methods for producing **rAAV** (claimed). The **rAAV** viruses can be used as vectors for somatic gene therapy. The **rAAV** can be used for producing proteins, such as insulin, glucagon, growth hormone, and insulin-like growth factor I.

ADVANTAGE - The **rAAV** viruses overcome the problems of inefficiency, contamination and purification problems of prior art somatic gene therapy vectors.

Dwg.0/1

L9 ANSWER 2 OF 20 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD

ACCESSION NUMBER: 2000-594333 [56] WPIDS

DOC. NO. CPI: C2000-177532

TITLE: Producing recombinant adeno-associated viral preparations for biological and pharmaceutical use, comprises producing the virus in a **Rep**, **Cap** and adenovirus helper function expressing cell culture.

DERWENT CLASS: B04 D16 J04

INVENTOR(S): CHADEUF, G; MOULLIER, P; NONY, P; SALVETTI, A

PATENT ASSIGNEE(S): (UYNA-N) UNIV NANTES

COUNTRY COUNT: 90

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000053788	A2	20000914	(200056)*	EN	66

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC
MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM
EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ
LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU
SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000053788 A2		WO 2000-EP1854	20000303

PRIORITY APPLN. INFO: US 1999-263093 19990305
AN 2000-594333 [56] WPIDS
AB WO 200053788 A UPAB: 20001106
NOVELTY - Producing **recombinant adeno-associated virus** (**rAAV**) preparations (I), comprising producing **rAAVs** in a cell culture expressing the **Rep** and **Cap** functions and adenovirus helper functions, and characterizing the **rAAVs** produced, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) characterizing an **rAAV** preparation comprises contacting a preparation sample with a culture of cells expressing **Rep** proteins, with a culture of cells expressing **Rep** proteins and co-infected with an adenovirus, and with culture of cells which do not express **Rep** protein but are co-infected with an adenovirus, and measuring the presence of virus in all three cultures;

(2) producing **rAAV** by:

(a) cotransfecting a cell culture with a **rAAV** vector plasmid, a **rep-cap** plasmid vector devoid of **inverted terminal repeats** (**ITR**), containing a **rep-cap** unit consisting of residues 190-4484 of AAV genome or fragments encoding functional **Rep** and **Cap** proteins, and an adenovirus plasmid containing the entire adenoviral genome or a genome lacking the left and right **ITRs**, the packaging region, and optionally the **E1** region, and recovering **rAAV** produced; or

(b) cotransfecting a culture of cells which contains nucleic acid constructs encoding **Rep** and **Cap** functions in their genome with a **rAAV** vector plasmid, a helper adenovirus, an adenovirus plasmid containing the entire adenoviral genome or a genome lacking the left and right **ITRs**, the packaging region, and optionally the **E1** region, and recovering **rAAV** produced;

(3) purifying **rAAVs** from a sample by performing cesium chloride density gradient centrifugation between 60000-70000 revolutions per minute (rpm), preferably for less than 12 hours, and recovering the fraction containing the purified **rAAV**, or by treating the sample by an anion exchange chromatography optionally combined with a heparin column and exclusion chromatography;

(4) an isolated Replication Encapsidation Sequence (RES) which is distinct from an AAV **ITR** sequence, and which provides or promotes the packaging of a nucleic acid sequence operably linked, into an AAV particle;

(5) a nucleic acid consisting of RES elements operably linked to a heterologous polynucleotide lacking a functional **ITR** sequence;

(6) a **rAAV** plasmid comprising a **recombinant AAV** genome and RES elements;

(7) a composition comprising a recombinant nucleic acid genome which comprises RES elements, in sense or antisense orientation;

(8) an AAV **Rep-Cap** plasmid devoid of a functional RES sequence; and

(9) the plasmids pspRC, pspRCC, pAdc and pAd Delta .

USE - For detecting the presence of **rAAV**, **Rep** -positive AAV and/or adenovirus in biological fluid (claimed), and for producing and testing high quality **rAAV** preparations, for biological, clinical, preclinical or pharmaceutical use. The **rAAV** characterization method is used in **rAAV** production and as a quality control in biological processes to the check quality of preparation.

ADVANTAGE - The characterizing method is transgene-independent, sensitive, accurate, and allows the measure of adenovirus and **recombinant AAV** contaminants. The method is suitable for any **rAAV** production or as a quality control in biological processes, to check the quality of preparation and optionally, allow the improvement of production parameters. The method is very efficient and provides immediate information regarding the quality of **rAAV** production. It can be used to monitor safety issues during preclinical, clinical or pharmaceuticals settings. The method provides not only the titer of preparation in infectious particles, regardless of the nature of heterologous nucleic acid contained in the vector, but also the level of contamination by adenoviruses and **rep**-positive **AAVs**. Use of plasmids such as pAd Delta in replacement of helper adenovirus does not reduce the yields of infectious **rAAV** particles produced. The use of the plasmids avoids the production of contaminating adenoviruses in the preparations.

Dwg.0/10

L9 ANSWER 3 OF 20 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-376571 [32] WPIDS
Searcher : Shears 308-4994

DOC. NO. CPI: C2000-113973
TITLE: Novel adeno-associated virus serotype 1 polynucleotide useful for preparation of medicament for delivery of a transgene to a host.
DERWENT CLASS: B04 D16
INVENTOR(S): WILSON, J M; XIAO, W
PATENT ASSIGNEE(S): (UYPE-N) UNIV PENNSYLVANIA
COUNTRY COUNT: 87
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000028061	A2	20000518	(200032)*	EN	108

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW

AU 2000018111	A	20000529	(200041)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000028061	A2	WO 1999-US25694	19991102
AU 2000018111	A	AU 2000-18111	19991102

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000018111	A Based on	WO 200028061

PRIORITY APPLN. INFO: US 1998-107114 19981105
AN 2000-376571 [32] WPIDS
AB WO 200028061 A UPAB: 20000706
NOVELTY - Adeno-associated virus serotype 1 (AAV-1) nucleotide comprising a sequence (s1) of 4718 bp as given in the specification, a DNA sequence (s2) complementary to (s1), cDNA (s3) complementary to (s1) or (s2), or an RNA complementary to (s1), (s2) or (s3), is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a polynucleotide (I) comprising an AAV-1 **inverted terminal repeat** (ITR) comprising a sequence (s4) comprising nucleotides 1-143 or 4576-4718 of (s1), a complementary sequence (s5) to (s4), or a functional fragment of (s4) or (s5);

(2) a **recombinant** vector (II) comprising a 5' **AAV**-1 / 3'**AAV**-1 **ITR** and the selected transgene;

(3) a nucleic acid molecule encoding AAV-1 helper functions, comprising an AAV **rep** coding region comprising nucleotides 335-2304 (**rep** 78), 335-2272 (**rep** 68, or the corresponding cDNA), 1007-2304 (**rep** 52), or nucleotides 1107-2272 (**rep** 40, or its corresponding cDNA) of (s1) and an AAV **cap** coding region, comprising nucleotides 2223-4431 (vp1), 2634-4432 (vp2) or 2829-4432 (vp3), of (s1);

(4) a host cell transduced with (II) or with an AAV-1 P5 **promoter** (AAV-1 functional fragment) comprising nucleotides 236-299 of (s1);

(5) a pharmaceutical composition comprising a virus containing (II);

(6) producing a selected gene product comprising transfecting a mammalian cell with AAV-1 or its functional fragment and culturing the cell under suitable conditions of expression; and

(7) delivering a transgene to a host through AAV-1 comprising:

(a) assaying a sample to determining the presence of neutralizing antibodies to AAV; and

(b) delivering an AAV virion comprising a capsid protein encoded by an AAV **cap** gene against which the host has no antibodies, and a transgene under the control of regulatory sequences and repeating the above procedure for several times.

USE - The AAV virion is useful for transforming host cells, and in the preparation of a medicament for the delivery of transgene to a host with no preexisting neutralizing antibodies against AAV-1 (all claimed).

ADVANTAGE - The AAV-1 does not induce the formation of neutralizing antibodies specific to any serotype of AAV.

DESCRIPTION OF DRAWING(S) - The diagram shows a 71 base pair homologous region among AASV-1 AAV-2 and AAV-6. Differing nucleotides are indicated by arrows.

Dwg.3B/6

L9 ANSWER 4 OF 20 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD

ACCESSION NUMBER: 2000-376523 [32] WPIDS

DOC. NO. CPI: C2000-113925

TITLE: Recombinant parvoviral vectors with altered packaging, tropisms and immunogenic properties, useful in gene therapy protocols.

DERWENT CLASS: B04 D16

INVENTOR(S): RABINOWITZ, J E; SAMULSKI, R J; XIAO, W

PATENT ASSIGNEE(S): (UYNC-N) UNIV NORTH CAROLINA

COUNTRY COUNT: 86

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG

WO 2000028004 A1 20000518 (200032)* EN 147
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC
MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES
FI GB GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR
LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI
SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW
AU 2000019111 A 20000529 (200041)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000028004 A1		WO 1999-US26505	19991110
AU 2000019111 A		AU 2000-19111	19991110

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000019111 A	Based on	WO 200028004

PRIORITY APPLN. INFO: US 1999-123651 19990310; US 1998-107840 19981110

AN 2000-376523 [32] WPIDS

AB WO 200028004 A UPAB: 20000706

NOVELTY - A hybrid virus particle (I) comprising a parvovirus capsid and an AAV (adeno-associated virus) genome packaged within the capsid, is new. If the parvovirus capsid is an AAV capsid, the serotypes of the AAV capsid and the AAV genome are different.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an isolated nucleic acid (II) encoding (I), comprising parvovirus **cap** (capsid) genes and AAV **rep** (repeat) genes (if the parvovirus **cap** genes are AAV **cap** genes, the serotype of the AAV **cap** genes and **rep** genes are different);

(2) a vector (III) comprising (II);

(3) a cell (IV) comprising (III);

(4) a method (V) of producing a hybrid virus particle, comprising providing a cell with AAV **rep** genes, parvovirus **cap** genes, an AAV genome and helper functions for generating a productive AAV infection (if the parvovirus **cap** genes are AAV **cap** genes, the serotypes of the AAV **cap** genes and the AAV genome are different);

(5) a hybrid virus particle (VI) produced by (V);

(6) a method (VI) of delivering a nucleic acid to a cell comprising introducing (I) into the cell;

(7) a method (VII) of administering a nucleic acid to a subject comprising administering (IV) and/or (I);

(8) a chimeric parvovirus capsid (VIII) comprise a **cap** region from an AAV virus and at least 1 capsid region from a B19 virus;

(9) an isolated nucleic acid (IX) encoding (VIII);

(10) a vector (X) comprising (IX); and

(11) a cell (XI) comprising (X).

ACTIVITY - None given.

MECHANISM OF ACTION - Nucleic acid vectors capable of delivering nucleic acids into cells.

No relevant data.

USE - (I) may be used in standard recombinant DNA protocols (e.g. gene therapy) as vectors for delivering nucleic acids to cells.

ADVANTAGE - The parvovirus packages larger than wild type AAV genomes and have altered antigenic properties and/or cellular tropisms (claimed).

Dwg.0/8

L9 ANSWER 5 OF 20 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD

ACCESSION NUMBER: 2000-246560 [21] WPIDS

DOC. NO. CPI: C2000-074631

TITLE: Producing high titers of **recombinant adenoassociated virus** comprising a therapeutic gene comprises infecting it and helper adenovirus comprising **E1**-deleted adeno virus genome into cells.

DERWENT CLASS: B04 D16

INVENTOR(S): MOUNTZ, J D; ZHANG, H

PATENT ASSIGNEE(S): (UABR-N) UAB RES FOUND

COUNTRY COUNT: 21

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000011149	A1	20000302	(200021)*	EN	83
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: AU CA JP					
AU 9956896	A	20000314	(200031)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000011149	A1	WO 1999-US19333	19990824
AU 9956896	A	AU 1999-56896	19990824

FILING DETAILS:

Searcher : Shears 308-4994

PATENT NO	KIND		PATENT NO
AU 9956896	A	Based on	WO 200011149

PRIORITY APPLN. INFO: US 1998-97666 19980824
AN 2000-246560 [21] WPIDS
AB WO 200011149 A UPAB: 20000502
NOVELTY - Producing (I) high titers of **recombinant adenoassociated virus** (**rAAV**) comprising therapeutic gene (Th) comprises infecting cells with **rAAV** with adenoviral inverted repeats flanking the therapeutic gene and **recombinant** helper adeno virus (rhAV) comprising an **E1**-deleted adeno virus genome and **AAV rep** and **cap** genes.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a method of producing high titers of **rAAV**-Th comprising infecting cells with a conditional packageable adenoviral helper vector, comprising genes encoding adenoviral packaging functions flanked by Loxp sequences, and at least one **rAAV** -Th, and purifying and titering the **rAAV**-Th; and

(2) **rAAV** comprising adenovirus genome and **rep** and **cap** genes flanked by AAV **inverted terminal repeats**.

ACTIVITY - Cytostatic; antisickling; antianemic; antiHIV.

MECHANISM OF ACTION - Gene therapy. No supporting data is given.

USE - The methods are useful for producing high titers of **rAAV** comprising therapeutic gene (claimed) which is useful in gene therapy for treating cancer and monogenic defects such as beta -thalassemia, sickle cell anemia, Fanconi anemia, chronic granulomatous disease, Gaucher disease, metachromatic leukodystrophy and cystic fibrosis, and Hodgkin's lymphoma, and human immunodeficiency virus (HIV) infection. **rAAV** produced by the methods is useful for diagnosis, disease monitoring and imaging (claimed).

ADVANTAGE - The method produces high titers of AAV (107 T.U./ml) compared to titers (104 T.U./ml) produced by conventional methods. The contamination of helper virus is also reduced.
Dwg.0/16

L9 ANSWER 6 OF 20 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-171020 [15] WPIDS
DOC. NO. CPI: C2000-053156
TITLE: New **recombinant** herpes virus useful in preparation of **recombinant adeno -associated virus** for gene therapy, contains **rep** and **cap**

Searcher : Shears 308-4994

adeno-associated genes.
DERWENT CLASS: B04 D16
INVENTOR(S): HEILBRONN, R; SCHETTER, C
PATENT ASSIGNEE(S): (HEIL-I) HEILBRONN R
COUNTRY COUNT: 22
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000001834	A1	20000113	(200015)*	GE	47
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: CA IL JP US					
DE 19830141	A1	20000113	(200015)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000001834	A1	WO 1998-EP5542	19980901
DE 19830141	A1	DE 1998-19830141	19980706

PRIORITY APPLN. INFO: DE 1998-19830141 19980706
AN 2000-171020 [15] WPIDS
AB WO 200001834 A UPAB: 20000323
NOVELTY - A **recombinant** herpes virus (I) containing **rep** and **cap** genes of **adeno-associated virus** (**AAV**) operably linked to an expression control sequence, is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) production of (I) by stable integration of the **rep** and **cap** genes into a herpes virus genome;
(2) a nucleic acid (II) that includes (I) and the helper functions of a herpes virus genome required for replication of AAV;
(3) a vector (III) containing (II);
(4) production of infectious AAV vector preparation (IV) by combining, in a cell, (I) and an AAV-based vector, replicating the vector and recovering (IV);
(5) cells (V) containing (I) or (III);
(6) production of (IV) by introducing, by infection, an AAV-vector and helper virus into a cell, replicating the vector and recovering (IV) from the cells and/or culture supernatant.
USE - (I) are used for production of AAV vector preparations (IV), which are used to deliver DNA in gene therapy.
ADVANTAGE - (I) provide high titers of infectious **AAV** vectors, they provide the helper functions (from **rep** and **cap**) required for efficient **AAV** replication and packaging. Herpes viruses are resistant to high levels of

Rep protein, and (I) are stable without reversion to the wild type (wt), and can be cultured to high titer (about 20% of that of wt). Production of **recombinant AAV** in herpes is not dependent on transfection efficiency, as when using plasmids.

DESCRIPTION OF DRAWING(S) - The drawing shows the structure of the **recombinant** herpes/**adeno-associated virus** genome.

Dwg.1/6

L9 ANSWER 7 OF 20 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-573148 [54] WPIDS
DOC. NO. CPI: C2000-171013
TITLE: Production of **recombinant adeno -associated virus**, useful e.g. for preparing tumor vaccines, comprises transfecting cells with helper and vector constructs at different times.
DERWENT CLASS: B04 D16
INVENTOR(S): HALLEK, M; HOERER, M
PATENT ASSIGNEE(S): (MEDI-N) MEDIGENE GES MOLEKULARBIOLOGISCHE DIAGNO; (MEDI-N) MEDIGENE AG
COUNTRY COUNT: 22
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
DE 19905501	A1	20000817	(200054)*		16
WO 2000047757	A1	20000817	(200054)	GE	
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: AU CA JP US					
AU 2000028039	A	20000829	(200062)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
DE 19905501	A1	DE 1999-19905501	19990210
WO 2000047757	A1	WO 2000-EP1090	20000210
AU 2000028039	A	AU 2000-28039	20000210

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000028039	A Based on	WO 200047757

PRIORITY APPLN. INFO: DE 1999-19905501 19990210
AN 2000-573148 [54] WPIDS
AB DE 19905501 A UPAB: 20001027

NOVELTY - Production of **recombinant adeno-associated virus** (**rAAV**) comprises treating suitable cells, at different times, with:

(i) at least one helper construct (HC) containing sequences encoding at least one **Rep** protein and/or the **Cap** protein; and

(ii) a vector construct (VC) containing sequences heterologous to AAV and flanked by **inverted terminal repeats** (**ITR**).

Preferably HC is introduced first.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) HC containing sequences that encode at least one **Rep** and **Cap** proteins, and preferably containing no nucleic acids, except AAV **promoters**, to which at least one **Rep** protein can bind specifically;

(2) VC containing one or more sequences heterologous to AAV, flanked by **ITR** which are in the flop orientation;

(3) tumor, particularly melanoma, cells (A), containing one or more heterologous nucleic acid sequences that encode granulocyte-macrophage colony stimulating factor (GM-CSF) and B7.2;

(4) pharmaceutical composition containing (A); and

(5) a method for the preparation of (A).

ACTIVITY - Antitumor.

MECHANISM OF ACTION - Immunostimulatory.

USE - **rAAv** are especially used to generate tumor, specifically melanoma, cells that contain heterologous sequences for expressing granulocyte-macrophage colony stimulating factor (GM-CSF) and B7.2. These cells are useful as vaccines for treating cancer, particularly melanoma. HC and VC are also useful for treating tumors, especially malignant melanoma or cancer of the ovary, breast, colon, prostate, head and neck. Very generally any therapeutic protein may be expressed from **rAAV**.

ADVANTAGE - Transfection with HC and VC at different times results in practically the same packaging efficiency as co-transfection, but because of the reduction in (non-)homologous **recombination** between the constructs, practically no wild-type **AAV** is formed, so purification of **rAAV** is much simplified. If HC is transfected first, the packaging efficiency is increased 1.5-3 times. In VC, when both inverse terminal repeats have the flop orientation, stability is improved, i.e. fewer **recombination** events occur.

Dwg.0/5

L9 ANSWER 8 OF 20 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-105885 [09] WPIDS
DOC. NO. CPI: C2000-031817
TITLE: Production of a recombinant vector for use in gene therapy to treat hemoglobinopathies, diabetes,

cancer, etc..
DERWENT CLASS: B04 D16
INVENTOR(S): PONNAZHAGAN, S; SRIVASTAVA, A; WANG, X
PATENT ASSIGNEE(S): (ADRE-N) ADVANCED RES & TECHNOLOGY INST
COUNTRY COUNT: 85
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9964569	A1	19991216	(200009)*	EN	100

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW

AU 9945587	A	19991230	(200022)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9964569	A1	WO 1999-US13070	19990609
AU 9945587	A	AU 1999-45587	19990609

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9945587	A	Based on	WO 9964569

PRIORITY APPLN. INFO: US 1998-88714 19980610
AN 2000-105885 [09] WPIDS
AB WO 9964569 A UPAB: 20000218
NOVELTY - Producing **adeno-associated virus** (**AAV**) particles by cotransfecting a cell with a **recombinant AAV** plasmid (I) and a helper plasmid encoding **rep** and **cap** polypeptide (II), both lacking homology in distal D sequence, is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS area so also included for the following:
(1) a method for reducing wild-type **AAV**-like particles in a **recombinant AAV** population, comprising providing an **AAV** plasmid lacking distal D sequences, and introducing the **AAV** plasmid into a cell along with a helper plasmid encoding **rep** and **cap** polypeptides, under replication conditions; and
(2) a population of AAV particles comprising (I) and having less than 3% of wild type (wt) AAV-like particles in it.

USE - The method is used to produce **recombinant** **AAV** population which have reduced wt **AAV** like particles (claimed). **Recombinant** vCMVp-lacZ vector stocks generated by cotransfecting pCMVp-lacZ(pD-20 having the wild type D sequence), or pBK-2 (pD-10) and pSP-19 were analyzed by quantitative DNA slot-blot. The results revealed contamination with wt **AAV**-like genomes was highest in vectors generated from plasmids pCMVp- lacZ+pSP-19 (0.8) and lowest in vectors generated from plasmids pBK-2+pSP-19 (0.1). The **AAV** particles produced are used as vectors for gene therapy in treating hemoglobinopathies, diabetes, cancer, etc.,

ADVANTAGE - The **recombinant** vector production method reduces the generation of wt **AAV** like particles and thus enables uncontaminated production of apathogenic **AAV**.

Dwg.0/11

L9 ANSWER 9 OF 20 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-062723 [05] WPIDS
DOC. NO. CPI: C2000-017510
TITLE: Adeno-associated viral vectors encapsidating a protein with adenovirus E4 ORF6 activity, useful for infecting target cells, particularly for gene therapy.
DERWENT CLASS: B04 D16
INVENTOR(S): ANDERSON, R J; MACDONALD, I D; PRENTICE, H G
PATENT ASSIGNEE(S): (UNLO) UNIV COLLEGE LONDON
COUNTRY COUNT: 20
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9961640	A2	19991202	(200005)*	EN	22

RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: JP US

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9961640	A2	WO 1999-GB1633	19990521

PRIORITY APPLN. INFO: GB 1998-11171 19980522
AN 2000-062723 [05] WPIDS
AB WO 9961640 A UPAB: 20000128
NOVELTY - Adeno-associated viral (AAV) vector containing a transgene and encapsidating a protein with adenovirus E4 ORF6 (I) activity, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for

the following:

(1) an AAV producer cell containing a gene encoding a protein with (I) activity, under the control of an inducible **promoter**; and

(2) production of an AAV vector comprising intoducing to a viral producer cell DNA comprising a transgene flanked by 2 AAV **inverted terminal repeats (ITRs**), and isolating the AAV vectors that formed.

USE - The AAV vectors can be used for infecting target cells, particularly in gene therapy.

ADVANTAGE - The presence of a protein with E4 ORF6 activity increases the level of expression of the transgene in target cells.

Dwg.0/0

L9 ANSWER 10 OF 20 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1999-302747 [25] WPIDS
DOC. NO. NON-CPI: N1999-226796
DOC. NO. CPI: C1999-088819
TITLE: Infectious helper viral particles for adeno-associated virus.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): ZHANG, X
PATENT ASSIGNEE(S): (CANT-N) CANTAB PHARM RES LTD
COUNTRY COUNT: 84
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9920778	A1	19990429	(199925)*	EN	37
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW					
AU 9894528	A	19990510	(199938)		
EP 1023452	A1	20000802	(200038)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9920778	A1	WO 1998-GB3114	19981019
AU 9894528	A	AU 1998-94528	19981019
EP 1023452	A1	EP 1998-947691	19981019
		WO 1998-GB3114	19981019

FILING DETAILS:

Searcher : Shears 308-4994

PATENT NO	KIND		PATENT NO
AU 9894528	A	Based on	WO 9920778
EP 1023452	A1	Based on	WO 9920778

PRIORITY APPLN. INFO: GB 1997-21909 19971017
AN 1999-302747 [25] WPIDS
AB WO 9920778 A UPAB: 19990630
NOVELTY - A preparation of infectious viral particles acting as helper virus for **adeno-associated virus** (**AAV**) contain DNA chosen for delivery to a target host cell and DNA for assembly and release of infectious **recombinant AAV** (**rAAV**). The **rAAV** are assembled on infection of a first target cell and released to infect a second target cell where they express the chosen DNA.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(a) a preparation of infectious **rAAV** genomes comprising heterologous DNA and packaged in AAV coat protein, produced by infection of a host cell with a preparation as above which is free of helper virus;

(b) a method of producing **rAAV** genomes as above, using a viral preparation as above; and

(c) a method of monitoring gene expression in a subject or in a culture of cells by administering the above infectious viral particles comprising a reporter gene for delivery and monitoring the cells for expression of the reporter gene.

ACTIVITY - Gene Therapy.

MECHANISM OF ACTION - Vector.

USE - The vector system is useful for gene delivery. The vector system is useful for immunostimulation by gene delivery of cytokine genes, antigen genes or immunomodulatory protein genes. The vectors can be used to deliver genes to replace a defective or missing gene in a target cell. Vectors containing reporters can be used to monitor the expression of genes. (all claimed)

ADVANTAGE - The vector system provides gene delivery and expression of DNA in cells that are not initially infected by viral particles of the preparation itself. These cells are therefore not the (primary) target of any immune response against the viral particles of the administered preparation, e.g. an anti-herpes immune response. The vectors generate high titer **recombinant adeno-associated virus** stocks that can be free or virtually free of helper virus contamination.

L9 ANSWER 11 OF 20 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1999-288312 [24] WPIDS
DOC. NO. CPI: C1999-085311
TITLE: Transcriptionally-activated Adeno-associated virus

inverted terminal repeat

DERWENT CLASS: B04 D16
INVENTOR(S): FELDHAUS, A L
PATENT ASSIGNEE(S): (TARG-N) TARGETED GENETICS CORP
COUNTRY COUNT: 84
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9920773	A2	19990429	(199927)*	EN	55
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW					
AU 9910966	A	19990510	(199938)		
EP 1025243	A2	20000809	(200039)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9920773	A2	WO 1998-US21937	19981020
AU 9910966	A	AU 1999-10966	19981020
EP 1025243	A2	EP 1998-953639	19981020
		WO 1998-US21937	19981020

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9910966	A	Based on	WO 9920773
EP 1025243	A2	Based on	WO 9920773

PRIORITY APPLN. INFO: US 1997-955400 19971021
AN 1999-288312 [24] WPIDS
AB WO 9920773 A UPAB: 19990719
NOVELTY - A polynucleotide comprising a transcriptionally-activated Adeno-associated virus (AAV) **inverted terminal repeat** (**ITR**) is new.
DETAILED DESCRIPTION - A new polynucleotide comprises a transcriptionally-activated Adeno-associated virus (AAV) **inverted terminal repeat** (**ITR**), where the **ITR** is less than about 400 bp in length and comprises a heterologous transcriptionally active element, and the **ITR** exhibits at least about a 2-fold increase in

transcriptional activity relative to a wild-type **ITR** under conditions permissive for transcription. INDEPENDENT CLAIMS are also included for:

(a) a polynucleotide (PN) comprising, in order a transcriptionally-activated **ITR** as above and a second **ITR** chosen from a wild-type **ITR**, a transcriptionally-activated **ITR**, a D sequence, a trs or a portion of a wild-type **ITR**;

(b) a plasmid comprising PN as in (a), further comprising an element selected from the group of an origin of replication and a reporter gene;

(c) a polynucleotide as above, further comprising a gene operably linked to the transcriptionally-activated **ITR**;

(d) an AAV viral particle comprising any polynucleotide as above;

(e) a mammalian cell comprising a polynucleotide as above; and

(f) a method of packaging a **recombinant AAV** vector.

ACTIVITY - Gene therapy.

MECHANISM OF ACTION - Vector.

USE - The transcriptionally-activated **inverted terminal repeats** (**ITR**) are useful for production of improved **recombinant adeno-associated virus** (**AAV**) vectors for in vivo gene transfer. The **AAV** vectors are particularly useful for packaging of large transgenes, especially the cystic fibrosis transmembrane conductance regulator (CFTR) gene for treatment of cystic fibrosis.

ADVANTAGE - The transcriptionally-activated **ITRs** enable construction of improved **rAAV** constructs in which transgene expression can be further elevated, despite potential vector size constrains. The new vectors provide high efficiency particle production and enhanced expression of the inserted transgenes. The **ITRs** exhibit at least about a 2-fold to 50-fold increases in transcriptional activity relative to wild-type **ITRs**.

Dwg.2/2

L9 ANSWER 12 OF 20 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1999-264033 [22] WPIDS
DOC. NO. CPI: C1999-077935
TITLE: New recombinant adeno-associated vectors.
DERWENT CLASS: B04 D16
INVENTOR(S): PONNAZHAGAN, S; SRIVASTAVA, A
PATENT ASSIGNEE(S): (ADRE-N) ADVANCED RES & TECHNOLOGY INST
COUNTRY COUNT: 83
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG

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     ------------------------------------------
     WO 9918227    A1 19990415 (199922)* EN   74
        RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC
            MW NL OA PT SD SE SZ UG ZW
         W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI
            GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT
            LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL
            TJ TM TR TT UA UG US UZ VN YU ZW
     AU 9912696    A  19990427 (199936)
     EP 1027451    A1 20000816 (200040)  EN
         R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

APPLICATION DETAILS:

     PATENT NO   KIND                  APPLICATION      DATE
     ------------------------------------------------------------
     WO 9918227    A1                  WO 1998-US21202  19981008
     AU 9912696    A                   AU 1999-12696    19981008
     EP 1027451    A1                  EP 1998-956097   19981008
                                       WO 1998-US21202  19981008

FILING DETAILS:

     PATENT NO   KIND                  PATENT NO
     ------------------------------------------------
     AU 9912696    A  Based on         WO 9918227
     EP 1027451    A1 Based on         WO 9918227

PRIORITY APPLN. INFO: US 1997-61364    19971008
AN   1999-264033 [22]   WPIDS
AB   WO   9918227 A UPAB: 19990609
     NOVELTY - New recombinant adeno-associated vectors
     comprise a promoter and a selected DNA sequence located
     between 2 adeno-associated virus
     inverted terminal repeats.
          DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included
     for:
          (1) a novel expression vector which comprises 2
     adeno-associated virus (AAV) inverted terminal
     repeats (ITRs) and an expression cassette
     comprising a selected DNA sequence and a promoter active
     in eukaryotic cells, where the cassette is located between the
     ITRs, the selected DNA sequence is operably linked to the
     promoter, and the vector lacks any AAV structural genes;
          (2) a B19 viral particle comprising an expression vector
     comprising 2 AAV ITRs and an expression cassette
     comprising a selected DNA sequence and a promoter active
     in eukaryotic cells, where the cassette is located between the
     ITRs, the selected DNA sequence is operably linked to the
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promoter, and the vector lacks any AAV structural genes;

(3) a helper virus construct comprising 2 adenovirus **inverter terminal repeats**, an AAV **rep** gene and a B19 VP2 **cap** gene, where the **rep** and **cap** genes are under the control of at least one **promoter** and are located between the **ITRs**;

(4) a method for packaging an AAV expression vector comprising:

(a) providing an expression vector comprising 2 AAV **ITRs** and an expression cassette comprising a selected DNA sequence and a **promoter** active in eukaryotic cells, where the cassette is located between the **ITRs**, where the selected DNA sequence is operably linked to the **promoter**, and the vector lacks any AAV structural genes;

(b) providing a helper virus construct comprising 2 adenovirus **ITRs**, an AAV **rep** gene and a B19 VP2 gene, where the **rep** and **cap** genes are under the control of at least one **promoter** and are located between the **ITRs**;

(c) contacting the expression vector and the helper virus construct with a host cell under conditions permitting the uptake of the expression vector and the helper virus construct by the cell;

(d) infecting the transfected host cell with adenovirus; and

(e) harvesting B19 particles from the host cell;

(5) a method for expressing a selected DNA sequence in a host cell comprising:

(a) providing a B19 viral particle comprising an expression vector comprising 2 AAV **ITRs** and an expression cassette comprising a selected DNA sequence and a **promoter** active in eukaryotic cells, where the cassette is located between the **ITRs**, the selected DNA sequence is operably linked to the **promoter**, and the vector lacks any AAV structural genes;

(b) contacting the viral particle with the host cell under conditions permitting infection of the host cell; and

(c) culturing the host cell under conditions permitting the transcription of the DNA sequence.

USE - The system can specifically target primitive progenitor and differentiated cells of the erythroid lineage, and can achieve stable integration and expression of transduced genes. The vectors can be used for the in vitro or in vivo delivery of genes to cells such as bone marrow cells, peripheral blood cells, endothelial cells and myocardial cells (claimed).

Dwg.0/6

L9 ANSWER 13 OF 20 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1999-244430 [20] WPIDS
DOC. NO. CPI: C1999-071404
TITLE: New **recombinant adeno-associated viruses**.

Searcher : Shears 308-4994

DERWENT CLASS: B04 D16
INVENTOR(S): GAO, G; WILSON, J M
PATENT ASSIGNEE(S): (UYPE-N) UNIV PENNSYLVANIA
COUNTRY COUNT: 83
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9915685	A1	19990401	(199920)*	EN	45
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW					
AU 9893970	A	19990412	(199934)		
EP 1015619	A1	20000705	(200035)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9915685	A1	WO 1998-US19463	19980918
AU 9893970	A	AU 1998-93970	19980918
EP 1015619	A1	EP 1998-947114	19980918
		WO 1998-US19463	19980918

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9893970	A	Based on	WO 9915685
EP 1015619	A1	Based on	WO 9915685

PRIORITY APPLN. INFO: US 1997-59340 19970919
AN 1999-244430 [20] WPIDS
AB WO 9915685 A UPAB: 19990525
NOVELTY - A cell with adeno-associated virus (AAV) **rep** gene and an AAV **cap** gene allows high level production of AAV.

DETAILED DESCRIPTION - A novel cell comprises an adeno-associated virus (AAV) **rep** gene and an AAV **cap** gene stably integrated within the cell's chromosomes, where the AAV **rep** and **cap** genes are each operatively linked to regulatory sequences capable of directing the expression of the **rep** and **cap** genes, and where the cell expresses gene products of the **rep** and **cap** genes upon introduction to the cell of a helper, the

helper comprising a member selected from a helper virus, a helper gene, and a helper product.

INDEPENDENT CLAIMS are also included for:

(1) a method for producing a helper-containing host cell comprising introducing to a host cell a helper, the host cell comprising an AAV **rep** gene and an AAV **cap** gene stably integrated within the host cell's chromosomes, where the AAV **rep** and **cap** genes are each under the control of regulatory sequences capable of directing the expression of the **rep** and **cap** genes, and where the host cell expresses gene products of the **rep** and **cap** genes upon introduction to the host cell of the helper, the helper comprising a member selected from a helper virus, a helper gene, and a helper gene product;

(2) a method for producing **recombinant AAV** comprising introducing to the helper-containing host cell as in (1) a **recombinant** hybrid virus comprising:

(a) a selected transgene operatively linked to regulatory sequences controlling the transgene's expression, the transgene with linked regulatory sequences being flanked by:

(b) AAV sequences comprising the 5' and 3' **ITRs** of an AAV, where the 5' **ITR** flanks one side of the transgene, and the 3' **ITR** flanks the other side, and where the transgene with linked regulatory sequences and with flanking AAV sequences is flanked by:

(c) at least one adenovirus cis-element selected from cis elements required for replication of adenovirus virions and cis elements required for encapsidation of adenovirus virions; where **recombinant AAV** is produced by the cell.

USE - The products and methods can be used to produce **recombinant AAV** (**rAAV**) which can be used in gene therapy to carry transgenes to correct a defect in a cell to modulate or alleviate the symptoms associated with the defect. These **rAAV** are useful as research reagents, as tools for the **recombinant** production of a transgene product in vitro, and as tools for the production of gene therapy reagents.

ADVANTAGE - The cell lines produced can provide level expression of **rAAV** (e.g. at least 1x103 **rAAV** particles/cell) upon the introduction of the helper to the cell line in comparison to the yields of **rAAV** from other stably **rep/cap** transfected cells.

Dwg.0/3

L9 ANSWER 14 OF 20 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1999-244041 [20] WPIDS
DOC. NO. CPI: C1999-071227
TITLE: Production of **recombinant adeno -associated virus**.
DERWENT CLASS: B04 D16

Searcher : Shears 308-4994

INVENTOR(S): WILSON, J M; XIAO, W
PATENT ASSIGNEE(S): (UYPE-N) UNIV PENNSYLVANIA
COUNTRY COUNT: 82
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9914354	A1	19990325	(199920)*	EN	37

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW

AU 9893191	A	19990405	(199933)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9914354	A1	WO 1998-US19479	19980918
AU 9893191	A	AU 1998-93191	19980918

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9893191	A	Based on	WO 9914354

PRIORITY APPLN. INFO: US 1997-59330 19970919
AN 1999-244041 [20] WPIDS
AB WO 9914354 A UPAB: 19990525
NOVELTY - High titers of **recombinant adeno-associated virus** (**rAAV**) are produced in host cells by transformation with constructs in which the expression of the rep78 and rep68 gene products are reduced and expression of rep52, rep40 and the **cap** gene products are kept at normal levels.

DETAILED DESCRIPTION - A recombinant host cell contains:

(a) a first nucleic acid molecule comprising, from 5' to 3', a parvovirus P5 **promoter**, a spacer, an AAV **rep** sequence and an AAV **cap** gene sequence, where the spacer is large enough to reduce expression of the rep78 and rep68 gene products relative to other **rep** gene products;

(b) a second nucleic acid molecule containing a minigene comprising a transgene flanked by AAV inverse terminal repeats (**ITRs**), under the control of regulatory sequences directing expression thereof in a host cell; and

(c) helper functions essential to the replication and packaging

or **rAAV**.

INDEPENDENT CLAIMs are also included for the following:

(1) a method for producing **rAAV**, comprising culturing a recombinant host cell as defined above, and isolating from the cell or cell culture a **rAAV** capable of expressing the transgene; and

(2) the nucleic acid of (a).

USE - The **recombinant adeno-associated viruses** (**rAAVs**) are useful for transferring therapeutic transgenes to a host cell or tissue. The **rAAVs** are also important as research agents, or as tools for the **recombinant** production of a transgene product in vitro.

ADVANTAGE - The limiting step for high yield of **recombinant adeno-associated virus** (**rAAV**) is not the cis plasmid used in the prior art, but the packaging process. Rep78 and rep68 gene products interfere with the packaging process, and so decreasing expression of these genes allows the production of **rAAV** to high titers.

Dwg.0/2

L9 ANSWER 15 OF 20 MEDLINE

ACCESSION NUMBER: 1999099022 MEDLINE
DOCUMENT NUMBER: 99099022
TITLE: Cloning and characterization of adeno-associated virus type 5.
AUTHOR: Chiorini J A; Kim F; Yang L; Kotin R M
CORPORATE SOURCE: Molecular Hematology Branch, National Heart, Lung and Blood Institute, Bethesda, Maryland 20892, USA.
SOURCE: JOURNAL OF VIROLOGY, (1999 Feb) 73 (2) 1309-19. Journal code: KCV. ISSN: 0022-538X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
OTHER SOURCE: GENBANK-AF085716
ENTRY MONTH: 199904
ENTRY WEEK: 19990403

AB **Adeno-associated virus** type 5 (AAV5) is distinct from other dependovirus serotypes based on DNA hybridization and serological data. To better understand the biology of AAV5, we have cloned and sequenced its genome and generated **recombinant** AAV5 particles. The single-stranded DNA genome is similar in length and genetic organization to that of AAV2. The **rep** gene of AAV5 is 67% homologous to AAV2, with the majority of the changes occurring in the carboxyl and amino termini. This homology is much less than that observed with other reported **AAV** serotypes. The **inverted terminal**

repeats (**ITRs**) are also unique compared to those of the other **AAV** serotypes. While the characteristic **AAV** hairpin structure and the **Rep** DNA binding site are retained, the consensus terminal resolution site is absent. These differences in the **Rep** proteins and the **ITRs** result in a lack of cross-complementation between AAV2 and AAV5 as measured by the production of **recombinant AAV** particles. Alignment of the **cap** open reading frame with that of the other **AAV** serotypes identifies both conserved and variable regions which could affect tissue tropism and particle stability. Comparison of transduction efficiencies in a variety of cells lines and a lack of inhibition by soluble heparin indicate that AAV5 may utilize a distinct mechanism of uptake compared to AAV2.

L9 ANSWER 16 OF 20 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1998-193636 [17] WPIDS
DOC. NO. CPI: C1998-062073
TITLE: **Recombinant adeno-associated virus** (**AAV**) - comprises T7 polymerase, **AAV** rev and **cap** genes and **AAV** inverted repeats flanking trans-gene of interest, used in, e.g. genetic engineering.
DERWENT CLASS: B04 D16
INVENTOR(S): CHEN, N; WILSON, J M
PATENT ASSIGNEE(S): (UYPE-N) UNIV PENNSYLVANIA
COUNTRY COUNT: 79
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9810088	A1	19980312	(199817)*	EN	43
RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW					
AU 9741833	A	19980326	(199832)		
EP 931158	A1	19990728	(199934)	EN	
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
AU 722624	B	20000810	(200043)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9810088	A1	WO 1997-US15716	19970904

Searcher : Shears 308-4994

AU 9741833	A	AU 1997-41833	19970904
EP 931158	A1	EP 1997-939829	19970904
		WO 1997-US15716	19970904
AU 722624	B	AU 1997-41833	19970904

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9741833	A	Based on	WO 9810088
EP 931158	A1	Based on	WO 9810088
AU 722624	B	Previous Publ.	AU 9741833
		Based on	WO 9810088

PRIORITY APPLN. INFO: US 1996-24699 19960906
AN 1998-193636 [17] WPIDS
AB WO 9810088 A UPAB: 19980428
Production of a **recombinant adeno-associated virus** (**AAV**) comprises: (a) introducing into a selected host cell: (i) a first vector comprising T7 polymerase operably linked to expression control sequences; (ii) a second vector comprising **AAV rep** and **cap** genes operably linked to T7 **promoter** sequences; (iii) a third vector comprising from 5' to 3', a cassette consisting of a 5' **AAV inverted terminal repeat** (**ITR**), a selected minigene and a 3' **AAV ITR**; (b) culturing the host cell under conditions permitting replication and packaging of **AAV**, and (c) recovering **AAV**. Also claimed is a **recombinant** adenovirus produced by the above method.
USE - The recombinant adenoviruses produced are useful as vectors in gene therapy and genetic engineering in general.
Dwg.0/4

L9 ANSWER 17 OF 20 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1998-193634 [17] WPIDS
DOC. NO. CPI: C1998-062071
TITLE: **Recombinant adeno-associated virus** (**AAV**) production - using cre **recombinase** and loxP sites; useful in genetic engineering and gene therapy.
DERWENT CLASS: B04 D16
INVENTOR(S): PHANEUF, D; WILSON, J M
PATENT ASSIGNEE(S): (UYPE-N) UNIV PENNSYLVANIA
COUNTRY COUNT: 79
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG

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     ------------------------------------------
     WO 9810086    A1 19980312 (199817)* EN   49
        RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL
            OA PT SD SE SZ UG ZW
         W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI
            GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD
            MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR
            TT UA UG US UZ VN YU ZW
     AU 9741830    A  19980326 (199832)
     EP 950111     A1 19991020 (199948)  EN
         R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
     AU 722375     B  20000803 (200042)
```

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9810086	A1	WO 1997-US15691	19970904
AU 9741830	A	AU 1997-41830	19970904
EP 950111	A1	EP 1997-939821	19970904
		WO 1997-US15691	19970904
AU 722375	B	AU 1997-41830	19970904

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9741830	A	Based on	WO 9810086
EP 950111	A1	Based on	WO 9810086
AU 722375	B	Previous Publ.	AU 9741830
		Based on	WO 9810086

PRIORITY APPLN. INFO: US 1996-25323 19960906

AN 1998-193634 [17] WPIDS

AB WO 9810086 A UPAB: 19980428

A method for the production of a **recombinant adeno -associated virus** (**AAV**) (A) with sufficient helper virus functions to express a transgene, comprises culturing a host cell containing and capable of expressing: (a) a cre transgene, which permits splicing out of the **rep** and **cap** gene inhibitory sequences, leading to the activation of **rep** and **cap**; (b) **AAV rep** and **cap** genes having a 5' spacer sequence flanked by lox sites; and (c) a minigene comprising a therapeutic transgene flanked by **AAV** inverse terminal repeats (**ITRs**).

Also claimed is a method for the production of a **recombinant AAV** (B) comprising: (a) a host cell expressing cre; (b) the introduction into the host cell of: (i) a first vector comprising, from 5' to 3', a **promoter**, a

spacer flanked by loxP sites and **AAV rep** and **cap** genes; (ii) a second vector comprising from 5' to 3', a minigene comprising a 5' **AAV ITR**, a **promoter**, a transgene and a 3' **AAV ITR**; (c) the culturing of the host cell under conditions which permit the expression of the cre **recombinase** and replication and packaging of the **recombinant AAV**; and (d) the recovery of the **recombinant AAV** capable of expressing the transgene product.

Recombinant AAVs produced using the above methods are also claimed.

USE - The recombinant adenoviruses produced are useful as vectors in gene therapy and genetic engineering in general.

Dwg.0/7

L9 ANSWER 18 OF 20 SCISEARCH COPYRIGHT 2000 ISI (R)
ACCESSION NUMBER: 97:159975 SCISEARCH
THE GENUINE ARTICLE: WH938
TITLE: Lack of site-specific integration of the **recombinant adeno-associated virus** 2 genomes in human cells
AUTHOR: Ponnazhagan S; Erikson D; Kearns W G; Zhou S Z; Nahreini P; Wang X S; Srivastava A (Reprint)
CORPORATE SOURCE: INDIANA UNIV, SCH MED, DEPT MICROBIOL & IMMUNOL, 635 BARNHILL DR, MS-255, INDIANAPOLIS, IN 46202 (Reprint); INDIANA UNIV, SCH MED, DEPT MICROBIOL & IMMUNOL, INDIANAPOLIS, IN 46202; INDIANA UNIV, SCH MED, DEPT MED, DIV HEMATOL ONCOL, INDIANAPOLIS, IN 46202; INDIANA UNIV, SCH MED, WALTHER ONCOL CTR, INDIANAPOLIS, IN 46202; EASTERN VIRGINIA MED SCH, JONES INST REPROD MED, CTR PEDIAT RES, NORFOLK, VA 23501; JOHNS HOPKINS UNIV, SCH MED, CTR MED GENET, BALTIMORE, MD 21287
COUNTRY OF AUTHOR: USA
SOURCE: HUMAN GENE THERAPY, (10 FEB 1997) Vol. 8, No. 3, pp. 275-284.
Publisher: MARY ANN LIEBERT INC PUBL, 2 MADISON AVENUE, LARCHMONT, NY 10538.
ISSN: 1043-0342.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 50
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The **adeno-associated virus** 2 (**AAV**)-based vector system has been suggested for its potential use in human gene therapy because the wild-type (wt) **AAV** genome appears to integrate into the human chromosomal

DNA in a site-specific manner. We systematically investigated the integration patterns of the **recombinant AAV** genomes lacking one or both the viral coding sequences. Four **recombinant AAV** genomes were constructed containing the genes for resistance to tetracycline (Tc-R) and the herpesvirus thymidine kinase (TK) **promoter**-driven gene for resistance to neomycin (neo(R); vTc.Neo), the genes for resistance to ampicillin (Ap(R)) and TK-neo(R) (vAp.Neo), the genes for **AAV** replication (**rep**) genes and TK-neo(R) (vRep.Neo), and the **AAV** capsid (**cap**) genes and TK-neo(R) (vCap.Neo). The integration pattern of each of the **recombinant AAV** genomes in individual clonal isolates of the human nasopharyngeal carcinoma cell line (KB) analyzed on Southern blots using a nea-specific DNA probe was distinctly different. In addition, in none of the clones examined was the proviral genome covalently linked to the previously described **AAV** right-junction (Rt.Jn.) human chromosomal DNA fragment, the putative specific-site of integration for the wt **AAV** genome. Furthermore, whereas a 276-bp DNA fragment could be readily amplified from each of these clones, using a neo-specific primer-pair by polymerase chain reaction (PCR), no amplified DNA product was obtained usign the neo- and the Rt.Jn. primer-pair under identical conditions. Fluorescence in situ hybridization (FISH) analyses further revealed the lack of integration of the **recombinant AAV** into human chromosome 19, even in the presence of a functional **rep** gene as determined by rescue of the **recombinant AAV** genome in the presence of adenovirus. These data suggest that the **recombinant AAV** genomes integrate at sites that are different from that characterized for the wt **AAV** genome. These studies may have implications in the development of the **AAV**-based vector system for its potential use in human gene therapy.

L9 ANSWER 19 OF 20 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1996-049697 [05] WPIDS
DOC. NO. CPI: C1996-016303
TITLE: **Recombinant adeno-associated virus** genome contg. protein encoding DNA - flanked by **inverted terminal repeats**, for use in vaccines or for treatment of neuro-degenerative disease.
DERWENT CLASS: B04 D16
INVENTOR(S): JOHNSON, P R
PATENT ASSIGNEE(S): (CHIL-N) CHILDRENS HOSPITAL INC
COUNTRY COUNT: 21
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9534670	A2	19951221	(199605)*	EN	45
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE					
W: AU CA JP					
AU 9531243	A	19960105	(199614)		
WO 9534670	A3	19960613	(199633)		
EP 764213	A1	19970326	(199717)	EN	
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE					
US 5658785	A	19970819	(199739)		18
JP 10504185	W	19980428	(199827)		51
US 5786211	A	19980728	(199837)		
US 5858775	A	19990112	(199910)		
AU 710804	B	19990930	(199952)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9534670	A2		WO 1995-US7178	19950606
AU 9531243	A		AU 1995-31243	19950606
WO 9534670	A3		WO 1995-US7178	19950606
EP 764213	A1		EP 1995-927113	19950606
			WO 1995-US7178	19950606
US 5658785	A		US 1994-254358	19940606
JP 10504185	W		WO 1995-US7178	19950606
			JP 1996-502305	19950606
US 5786211	A	Div ex	US 1994-254358	19940606
			US 1995-475391	19950607
US 5858775	A	Div ex	US 1994-254358	19940606
			US 1996-709609	19960910
AU 710804	B		AU 1995-31243	19950606

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9531243	A	Based on	WO 9534670
EP 764213	A1	Based on	WO 9534670
JP 10504185	W	Based on	WO 9534670
US 5786211	A	Div ex	US 5658785
US 5858775	A	Div ex	US 5658785
AU 710804	B	Previous Publ.	AU 9531243
		Based on	WO 9534670

PRIORITY APPLN. INFO: US 1994-254358 19940606; US 1995-475391 19950607; US 1996-709609 19960910

AN 1996-049697 [05] WPIDS

AB WO 9534670 A UPAB: 19960205

Searcher : Shears 308-4994

A **recombinant adeno-associated virus (AAV)** genome contains **AAV inverted terminal repeats (ITR)** flanking a DNA sequence (I) at encodes (a) an immunodeficiency virus protein (A) or (b) one of tyrosine hydroxylase, aromatic amino acid decarboxylase, nerve growth factor, brain derived neurotrophic factor, NT-3, NT-4/5, glial derived neurotrophic factor or fibroblast growth factor, operably linked to functional **promoter** and polyadenylation sequence. Also claimed are: (1) DNA vectors contg. this **recombinant AAV** genome; (2) mammalian host cells stably transformed with this **recombinant AAV** genome and **AAV rep-cap** genes; (3) prodn. of infectious **recombinant AAV** by infecting these cells with an **AAV** helper virus; and (4) infectious **recombinant AAV** produced this way.

USE - The infectious recombinant viruses are used to deliver DNA to cells, esp. (i) as vaccines against HIV infection and (ii), where (I) encodes one of the proteins specified in (b), for treatment of neurodegenerative diseases, specifically Alzheimer's, Parkinson's and Huntington's diseases. Also (not claimed) where (I) encodes a cpd. other than those specified, the recombinant viruses can be used to treat of variety of other diseases.

Dwg.0/5

ABEQ US 5658785 A UPAB: 19970926

A mammalian host cell stably transfected with a **recombinant adeno-associated virus** genome and with **adeno-associated virus rep-cap** genes.

Dwg.0/5

L9 ANSWER 20 OF 20 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD

ACCESSION NUMBER: 1995-115457 [15] WPIDS

DOC. NO. CPI: C1995-052676

TITLE: Novel adenovirus or herpes virus construct - useful for prodn. of **recombinant adeno-associated virus** virion(s) e.g. for human gene therapy applications.

DERWENT CLASS: B04 D16

INVENTOR(S): DONG, J; FRIZZELL, R A

PATENT ASSIGNEE(S): (UABR-N) UAB RES FOUND

COUNTRY COUNT: 19

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9506743	A2	19950309	(199515)*	EN	90

RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE

W: AU CA JP

AU 9475656 A 19950322 (199527)
WO 9506743 A3 19951012 (199621)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9506743	A2	WO 1994-US9205	19940816
AU 9475656	A	AU 1994-75656	19940816
WO 9506743	A3	WO 1994-US9205	19940816

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9475656	A	Based on	WO 9506743

PRIORITY APPLN. INFO: US 1993-114595 19930831
AN 1995-115457 [15] WPIDS
AB WO 9506743 A UPAB: 19950425
The following are claimed: (1) an adenovirus or herpes virus vector construct (I) comprising a **recombinant** insert including an expression region comprising an essential **adeno-associated virus** (**AAV**) gene, the vector expressing an essential **AAV** protein; (2) a **recombinant** adenovirus or herpes virus virion which includes a **recombinant** vector transcription unit capable of expressing an essential **AAV** protein; (3) a **recombinant** adenovirus or herpes virus virion which includes a **recombinant** vector transcription unit capable of expressing an essential **AAV** protein, an adenovirus or herpes virus vector construct comprising a **recombinant** insert including an **AAV** vector comprising **AAV ITR** sequences and an expression region encoding a **recombinant** protein, the **AAV** vector being capable of integrating into a host cell genome, a **recombinant** adenovirus or herpes virus virion which contains a vector construct comprising a **recombinant** insert which includes an **AAV** vector comprising **AAV ITR** sequences a nd a transcription unit encoding a **recombinant** protein, the **AAV** vector being capable of integrating into a host cell genome and expressing a **recombinant** proteins, and an **AAV** producer cell comprising a stably integrated **recombinant AAV** vector which includes **AAV ITR** sequences and an expression region encoding a full length CFTR protein, the cell being capable of producing **recombinant AAV** virions bearing a full length CFTR gene when contacted with replication-deficient adenovirus or herpes virus particles which include a vector capable of expressing an

essential **AAV** protein. Method for producing **recombinant AAV** virions comprises introducing into a host cell a **recombinant AAV** vector, infecting the cell with **recombinant** adenovirus or herpes virus capable of expressing an essential **AAV** protein and culturing the cell to produce **AAV** virions. Claimed embodiment comprises (a) preparing a **recombinant** adenovirus or herpes virus which includes (I), (b) preparing a cell capable of producing **AAV** by introducing a **recombinant AAV** vector into a host cell, (c) infecting the cell with the **recombinant** virus in an amt. effective to stimulate the prodn. of **recombinant AAV** virions, and (d) culturing the infected cell to obtain the **recombinant AAV** virions. Prodn. of **recombinant AAV** virions comprises obtaining **recombinant AAV** virions from a cultured host cell infected with a **recombinant** adenovirus contg. a vector in which the **E1** region has been replaced with an **AAV** vector construct comprising an expression region encoding a selected protein, the **AAV** vector being capable of integrating into the host cell genome, a **recombinant** adenovirus contg. a vector in which the E3 region has been replaced with the **AAV rep**-lip genes, the vector expressing the lip protein, and a **recombinant** adenovirus contg. a vector in which the E3 region has been replaced with the **AAV cap** gene, the vector expressing the **cap** protein.

USE - The AAV produced has a variety of applications including for transferring exogenous genes into human cell lines and for use in human gene therapy regimes esp. for cystic fibrosis treatment Gene therapy treatment is esp. applicable to genetic diseases of the blood, such as sickle-cell anaemia, clotting disorders and thalassemias, inherited immune deficiency syndrome (ADA deficiency) and cystic fibrosis. Gene therapy may also prove useful in the treatment of cancer, diabetes, AIDs, hypercholesterolaemia, other disorders of the liver and lung and diseases associated with hormone deficiencies.

Dwg.3/9

FILE 'CAPLUS' ENTERED AT 15:59:02 ON 01 DEC 2000

L10	1677	SEA	ABB=ON	PLU=ON	(AAV OR (ADENOASSOC? OR ADENO ASSOC?)(W)VIRUS) OR RAAV
L11	160	SEA	ABB=ON	PLU=ON	L10 AND (ITR OR INVERT? TERMIN? REPEAT)
L12	35	SEA	ABB=ON	PLU=ON	L11 AND CAP
L13	35	SEA	ABB=ON	PLU=ON	L12 AND REP
L14	24	SEA	ABB=ON	PLU=ON	L13 AND (PROMOTER OR E1# OR E2#)
L15	4	SEA	ABB=ON	PLU=ON	L14 NOT L7

L15 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2000 ACS

Searcher : Shears 308-4994

ACCESSION NUMBER: 1999:790899 CAPLUS
DOCUMENT NUMBER: 132:31759
TITLE: Helper functions for **adeno-associated virus** for high-efficiency generation of wild-type-free virus carrying foreign genes
INVENTOR(S): Colosi, Peter
PATENT ASSIGNEE(S): Avigen, Inc., USA
SOURCE: U.S., 19 pp., Cont.-in-part of Ser. No. US 1998-107708, filed on 30 Jun 1998 which is
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6001650	A	19991214	US 1998-143270	19980828
US 5622856	A	19970422	US 1995-510790	19950803
US 6027931	A	20000222	US 1998-107708	19980630
PRIORITY APPLN. INFO.:			US 1995-510790	19950803
			US 1996-688648	19960729
			US 1998-107708	19980630

AB Helper functions for the packaging of **adeno-assocd**. **virus** (**AAV**) that do not allow the generation pseudowild **AAV** virions are described. The helper functions include the **AAV rep** and **cap** genes expressed from the p19 and p40 **promoters** but lacking a p5 **promoter** because of deletion of the p5 TATA box. In addn., **inverted terminal repeats** are deleted from expression constructs for the **rep** and **cap** genes. Host cells expressing these genes and the manuf. of transgenic virions are described. A helper plasmid of the invention, pHLP19, carrying the **rep** and **cap** genes and the p19 and p40 **promoters** gave a yield of **AAV** that was 200-300% greater than that from prior art helper vectors with no detectable generation of pseudowild type virus.

REFERENCE COUNT: 5
REFERENCE(S):
(1) Li; Journal of Virology 1997, V71(7), P5236 CAPLUS
(2) Ogasawara; Microbiol Immunol 1998, V42(3), P177 CAPLUS
(3) Samulski; Journal of Virology 1989, V63(9), P3822 CAPLUS
(4) Shenk; US 5436146 1995 CAPLUS
(5) Shenk; US 5753500 1998

Searcher : Shears 308-4994

L15 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:220078 CAPLUS
DOCUMENT NUMBER: 130:233247
TITLE: Expression vectors and host cells for the manufacture of **adeno-associated viruses** carrying foreign DNA
INVENTOR(S): Wilson, James M.; Xiao, Weidong
PATENT ASSIGNEE(S): The Trustees of the University of the Pennsylvania, USA
SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9914354	A1	19990325	WO 1998-US19479	19980918
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9893191	A1	19990405	AU 1998-93191	19980918
PRIORITY APPLN. INFO.:			US 1997-59330	19970919
			WO 1998-US19479	19980918

AB Host cells and expression vectors that can be used to manuf. **adeno-assocd. virus** carrying cloned genes in high titer are described. This is achieved by limiting the expression of the rep68 and rep78 genes without affecting the expression of the rep40 and rep52 and structural protein genes. An expression vector for the **rep** and **cap** genes uses the parvovirus P5 **promoter** to drive expression. The **promoter** is sepd. from the genes by a spacer that limits expression of the rep68 and rep78 genes. There are no particular sequence requirements for the spacer. A second vector carries a minigene of interest flanked by a pair of **AAV inverted terminal repeats**. Expts. detg. the lengths of spacer that give the greatest yield of virus are reported. A spacer of .ltoreq.500 base pairs gave the highest titer of virus although increased titers could be found with spacers of up to 3.8 kb.

REFERENCE COUNT: 6

REFERENCE(S):
(1) Allen, J; WO 9617947 A 1996
(2) Avigen Inc; WO 9706272 A 1997
(3) Graham, F; WO 9640955 A 1996
(4) Pennsylvania, U; WO 9810086 A 1998
(5) Sambrook, J; Molecular Cloning A laboratory manual 1989
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:176036 CAPLUS
DOCUMENT NUMBER: 128:214186
TITLE: Regulated control of **adeno-associated virus** replication using bacteriophage T7 **promoters** and regulated expression of the T7 polymerase gene
INVENTOR(S): Wilson, James M.; Chen, Nancie
PATENT ASSIGNEE(S): Trustees of the University of Pennsylvania, USA; Wilson, James M.; Chen, Nancie
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9810088	A1	19980312	WO 1997-US15716	19970904
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9741833	A1	19980326	AU 1997-41833	19970904
AU 722624	B2	20000810		
EP 931158	A1	19990728	EP 1997-939829	19970904
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRIORITY APPLN. INFO.:			US 1996-24699	19960906
			WO 1997-US15716	19970904

AB A method for efficient replication and packaging of **adeno-assocd. virus** vectors carrying foreign genes for use in gene therapy is described. The method avoids the toxicity problems assocd. with high levels of the **rep** gene product. The method uses three sep. expression constructs. One of these

carries an expression cassette for the T7 polymerase gene. The preferred **promoter** is the cytomegalovirus immediate-early **promoter**. A second carries the virus **rep** and **cap** genes under the control of T7 **promoters**. A third vector contains a cassette in which the **adeno-assocd. virus inverted terminal repeats** flank a minigene. Quiescent host cells carrying one or two of these vectors can be prepd. with introduction of the third vector inducing formation of virus.

L15 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:951301 CAPLUS
DOCUMENT NUMBER: 123:332111
TITLE: Integrative adenovirus expression vectors for use in gene therapy
INVENTOR(S): Denefle, Patrice; Latta, Martine; Perricaudet, Michel; Vigne, Emmanuelle
PATENT ASSIGNEE(S): Rhone-Poulenc Rorer S.A., Fr.
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9523867	A1	19950908	WO 1995-FR233	19950228
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, US, UZ, VN				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
FR 2716893	A1	19950908	FR 1994-2445	19940303
FR 2716893	B1	19960412		
CA 2184113	AA	19950908	CA 1995-2184113	19950228
AU 9518526	A1	19950918	AU 1995-18526	19950228
EP 748385	A1	19961218	EP 1995-910605	19950228
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 09509578	T2	19970930	JP 1995-522730	19950228
ZA 9501803	A	19960109	ZA 1995-1803	19950303
US 6033885	A	20000307	US 1996-702573	19960912
PRIORITY APPLN. INFO.:			FR 1994-2445	19940303
			WO 1995-FR233	19950228

AB Recombination-defective adenoviruses carrying a cassette that can be integrated into the genome of host cells are constructed for use in gene therapy. The cassette particularly contains at least one

inverted terminal repeat (ITR) of an **adeno-assocd. virus** (**AAV**) and a therapeutic gene. The use of the **AAV ITR** directs integration to the same locus in all cases and minimizes possible complications from random integration. The construction of virus carrying the lacZ reporter gene or a human lipoprotein AI gene under control of viral (vesicular stomatitis or Rous sarcoma virus) **promoters** is described.

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 16:01:27 ON 01 DEC 2000)

L16 20 S L14
L17 0 S L16 NOT L8

(FILE 'CAPLUS' ENTERED AT 16:02:33 ON 01 DEC 2000)

L18 38 S L11 AND TRANSGENE
L19 25 S L18 AND (PROMOTER OR E1# OR E2#)
L20 19 S L19 NOT (L7 OR L14)

L20 ANSWER 1 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 2000:318424 CAPLUS
DOCUMENT NUMBER: 133:218291
TITLE: Overcoming **adeno-associated virus** vector size limitation through viral DNA heterodimerization
AUTHOR(S): Sun, Liangwu; Li, Juan; Xiao, Xiao
CORPORATE SOURCE: Dep. Molecular Genetics and Biochem. & Gene Therapy Center & Duchenne Muscular Dystrophy Res. Center, Univ. Pittsburgh, Pittsburgh, PA, 15261, USA
SOURCE: Nat. Med. (N. Y.) (2000), 6(5), 599-602
CODEN: NAMEFI; ISSN: 1078-8956
PUBLISHER: Nature America Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Split **adeno-assocd. virus** (**AAV**) vectors (SAVE) consist of large **transgenes** split so as to fit into the **AAVs**. **Inverted terminal repeats** (**ITRs**) permit recombination of the **transgenes** in transfected cells to form concatamers. The use of eukaryotic RNA splicing signals cause removal of the **ITR** in pre-mRNA processing. One vector lacks a **promoter** and the other, a poly(A) signal so that unrecombined vectors do not transcribe partial **transgenes**. As an example, plasmids pAAVLacZ-5' and pAAVLacZ-3' with a human chorionic gonadotropin intron 1 are transfected into human 293 cells to produce .beta.-galactosidase after recombination, transcription, mRNA splicing, and translation.
REFERENCE COUNT: 26

REFERENCE(S):
(1) Cheung, A; J Virol 1980, V33, P739 CAPLUS
(2) Dong, J; Hum Gene Ther 1996, V7, P2101 CAPLUS
(3) Duan, D; J Virol 1998, V72, P8568 CAPLUS
(4) Duan, D; Virology 1999, V261, P8 CAPLUS
(5) Duan, D; erratum: J Virol 1999, V73, P861 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 2 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 2000:318422 CAPLUS
DOCUMENT NUMBER: 133:218290
TITLE: A new dual-vector approach to enhance recombinant **adeno-associated virus**-mediated gene expression through intermolecular cis activation
AUTHOR(S): Duan, Dongsheng; Yue, Yongping; Yan, Ziying; Engelhardt, John F.
CORPORATE SOURCE: Dep. Anatomy and Cell Biology, coll. Med., Univ. Iowa, Iowa City, IA, 52242, USA
SOURCE: Nat. Med. (N. Y.) (2000), 6(5), 595-598
CODEN: NAMEFI; ISSN: 1078-8956
PUBLISHER: Nature America Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Coinfection with one **adeno-assocd. virus** (**AAV**) vector contg. a **transgene** and another **AAV** vector contg. a **promoter** allow high expression of the **transgene** because of concatamerization of the vectors via recombination through **inverted terminal repeats**. Cis activation is demonstrated using this system in fibroblasts with luciferase as reporter gene. The SV40 poly(A) signal is located on the **transgene**-contg. vector and another vector contains the SV40 **promoter** sequence. Cis activation is also demonstrated to increase luciferase **transgene** expression in muscle in mice. Intermol. recombination is confirmed by Souhtern blot anal.
REFERENCE COUNT: 9
REFERENCE(S):
(1) Duan, D; J Virol 1998, V72, P8568 CAPLUS
(2) Duan, D; J Virol 1999, V73, P161 CAPLUS
(3) Duan, D; Virology 1999, V261, P8 CAPLUS
(4) Duan, D; Virus Res 1997, V48, P41 CAPLUS
(5) Flotte, T; J Biol Chem 1993, V268, P3781 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 3 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 2000:191240 CAPLUS
DOCUMENT NUMBER: 132:247147

TITLE: Adenovirus vector for heart-specific gene expression and its use in gene therapy

INVENTOR(S): Chien, Kenneth R.; Wang, Yibin; Evans, Sylvia
PATENT ASSIGNEE(S): Regents of the University of California, USA

SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000015821	A1	20000323	WO 1999-US20730	19990910
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9958195	A1	20000403	AU 1999-58195	19990910

PRIORITY APPLN. INFO.: US 1998-99960 19980911
WO 1999-US20730 19990910

AB A human type-5 recombinant adenovirus vector Ad/CG/**ITR** for heart-specific gene expression is constructed by using the **promoter** from the cardiomyocyte-restricted cardiac ankyrin repeat protein (CARP)in combination of the **inverted terminal repeat** (**ITR**) sequences from human **adeno-assocd. virus** (**AAV**). Using green fluorescent protein (GFP) as a marker gene, Ad/CG/**ITR** is shown to direct **transgene** expression to myocardial tissue in cultured cell lines, in the injected heart muscle and in developing mouse embryos (by microinjection into cardiac cavities). The inclusion of **AAV ITR** is required for tissue-specific expression and the gene expression is regulated at the transcription level. The **promoters** of other cardiac restricted genes are also suggested. These cardiac-specific adenovirus vector can be used in gene therapy of heart diseases.

REFERENCE COUNT: 8
REFERENCE(S):
(1) Arch Dev Corp; WO 9411506 A 1994
(2) Jeyaseelan, R; THE JOURNAL OF BIOLOGICAL CHEMISTRY 1997, V272(36), P22800 CAPLUS
(3) Philip, R; MOLECULAR AND CELLULAR BIOLOGY 1994, V14(4), P2411 CAPLUS
(7) Yeh, P; FASEB JOURNAL 1997, V11(8), P615

Searcher : Shears 308-4994

CAPLUS
(8) Zou, Y; DEVELOPMENT 1997, V124, P793 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 4 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:753368 CAPLUS
DOCUMENT NUMBER: 132:950
TITLE: **Adeno-associated virus** vectors utilizing splicing and gene therapy applications in airway and muscle tissue
INVENTOR(S): Engelhardt, John F.; Duan, Dongsheng
PATENT ASSIGNEE(S): University of Iowa Research Foundation, USA
SOURCE: PCT Int. Appl., 121 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9960146	A1	19991125	WO 1999-US11197	19990520
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9940912	A1	19991206	AU 1999-40912	19990520
PRIORITY APPLN. INFO.:			US 1998-86166	19980520
			US 1999-276625	19990325
			WO 1999-US11197	19990520

AB The invention provides an isolated and purified DNA mol. comprising at least one DNA segment, a biol. active subunit or variant thereof, of a circular intermediate of **adeno-assocd. virus**, which DNA segment confers increased episomal stability, persistence or abundance of the isolated DNA mol. in a host cell. The invention also provides a compn. comprising at least two **adeno-assocd. virus** vectors. This vector system has increased stability and/or persistence in host cells and is useful to express large open reading frames as shown in tibialis muscle. The **rAAV** circular concatamers were used to delivery trans-splicing vectors with large gene inserts. Two **rAAV** vectors encoding two halves of a cDNA flanked by splice site consensus sequences are described. Full-length

transgene mRNA is produced by splicing between these two vector-encoded sequences within circular concatamers. It was found that formation of head-to-tail circular **AAV** intermediates is augmented by superinfection with **E1**-deleted adenovirus during transduction. Long-term persistence of **transgene** expression in muscle was shown with these **AAV** circular intermediates. Evidence for increased episomal persistence of **AAV** circular intermediate in model for in utero plasmid-based gene therapy was shown. Liposome mediated transfer of vectors to airway and muscle were successful. Further this study relates delivery of multiple genes through intermol. concatamerization. This concatamerization is achieved through uniform intermol. recombination between **ITRs** of independent viral genomes. The adenovirus **E2A** protein is used to enhance episome stability. The CFTR -cystic fibrosis transmembrane conductance regulator protein may be effectively expressed using this system and targeted to specific tissue. This vector system therefore can be used to manuf. a medicament to treat a pathol. condition in a mammal.

REFERENCE COUNT: 12

REFERENCE(S):
(1) Duan, D; J Virology 1998, V72(11), P8568 CAPLUS
(2) Duan, D; J Virology 1999, V73(1), P161 CAPLUS
(3) Duan, D; Virology 1999, V261(1), P8 CAPLUS
(4) Duan, D; Virus Research 1997, V48(1), P41 CAPLUS
(5) Fisher, K; Nature Medicine 1997, V3(3), P306 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 5 OF 19 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1999:722791 CAPLUS
DOCUMENT NUMBER: 131:347488
TITLE: Packaging systems for human recombinant adenovirus to be used in gene therapy
INVENTOR(S): Vogels, Ronald; Bout, Abraham
PATENT ASSIGNEE(S): Introgene B.V., Neth.
SOURCE: Eur. Pat. Appl., 82 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 955373	A2	19991110	EP 1999-201278	19990423
EP 955373	A3	20000419		

Searcher : Shears 308-4994

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

AU 9934458	A1	19991116	AU 1999-34458	19990423
WO 9955132	A3	20000406	WO 1999-NL235	19990423

W: AU, CA, JP, MX, NZ

PRIORITY APPLN. INFO.:	US 1998-65752	19980424
	WO 1999-N	

L235 19990423

AB The invention discloses novel means and methods for the generation of adenovirus vectors. One method of the invention entails a method for generating an adenovirus vector comprising welding together two nucleic acid mols. whereby said mols. comprise partially overlapping sequences capable of combining with each other allowing the generation of a phys. linked nucleic acid comprising at least two functional adenovirus **inverted terminal repeats**, a functional encapsulation signal, and a nucleic acid of interest or functional parts, derivs., and/or analogs thereof. A novel packaging cell line, designated 911, is derived from diploid human embryonic retinoblasts (HER) that harbors nucleotides 80-6788 of the adenovirus 5 genome. Novel packaging cell lines are also provided that express just **E1A** genes and **E1B** genes without undergoing apoptotic cell death, as occurs in human diploid cells that express **E1A** in the absence of **E1B**, and are able to transcomplement **E1B**-defective recombinant adenoviruses. Packaging constructs that are mutated or deleted for **E1B** 21-kDa, but just express the 55-kDa protein, and packaging constructs to be used for generation of complementing cell lines from diploid cells without the need of selection with marker genes are also provided. After transfection of HER cells with construct pIG.**E1A**. **E1B**, 7 independent cell lines could be established (designated PER.C1 to PER.C9) which express **E1A** and **E1B** proteins, are stable, and complement **E1** -defective adenovirus vectors. New adenovirus vectors are provided with extended **E1** deletions but contain pIX **promoter** sequences and the pIX gene, and are the basis for the development of further deleted adenovirus vectors that are mutated for **E2A**, **E2B**, or E4.

L20 ANSWER 6 OF 19 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER:	1999:675882 CAPLUS
DOCUMENT NUMBER:	132:45541
TITLE:	Integrating adenovirus-**adeno-associated virus** hybrid vectors devoid of all viral genes
AUTHOR(S):	Lieber, Andre; Steinwaerder, Dirk S.; Carlson, Cheryl A.; Kay, Mark A.
CORPORATE SOURCE:	Division of Medical Genetics, University of Washington, Seattle, WA, 98195, USA

Searcher : Shears 308-4994

SOURCE: J. Virol. (1999), 73(11), 9314-9324
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recently, we demonstrated that inverted repeat sequences inserted into first-generation adenovirus (Ad) vector genomes mediate precise genomic rearrangements resulting in vector genomes devoid of all viral genes that are efficiently packaged into functional Ad capsids. As a specific application of this finding, we generated adenovirus-**adeno-assocd. virus** (**AAV**) hybrid vectors, first-generation Ad vectors contg. **AAV inverted terminal repeat** sequences (**ITRs**) flanking a reporter gene cassette inserted into the **E1** region. We hypothesized that the **AAV ITRs** present within the hybrid vector genome could mediate the formation of rearranged vector genomes (.DELTA.Ad. **AAV**) and stimulate **transgene** integration. We demonstrate here that .DELTA.Ad.**AAV** vectors are efficiently generated as byproducts of first-generation adenovirus-**AAV** vector amplification. .DELTA.Ad.**AAV** genomes contain only the **transgene** flanked by **AAV ITRs**, Ad packaging signals, and Ad **ITRs**. .DELTA.Ad.**AAV** vectors can be produced at a high titer and purity. In vitro transduction properties of these deleted hybrid vectors were evaluated in direct comparison with first-generation Ad and recombinant **AAV** vectors (**rAAVs**). The .DELTA.Ad.**AAV** hybrid vector stably transduced cultured cells with efficiencies comparable to **rAAV**. Since cells transduced with .DELTA.Ad.**AAV** did not express cytotoxic viral proteins, hybrid viruses could be applied at very high multiplicities of infection to increase transduction rates. Southern anal. and pulsed-field gel electrophoresis suggested that .DELTA.Ad.**AAV** integrated randomly as head-to-tail tandems into the host cell genome. The presence of two intact **AAV ITRs** was crucial for the prodn. of hybrid vectors and for **transgene** integration. .DELTA.Ad.**AAV** vectors, which are straightforward in their prodn., represent a promising tool for stable gene transfer in vitro and in vivo.

REFERENCE COUNT: 41
REFERENCE(S):
(1) Alexander, I; Hum Gene Ther 1996, V7, P841 CAPLUS
(2) Balague, C; J Virol 1997, V71, P3299 CAPLUS
(3) Conway, J; J Virol 1997, V71, P8780 CAPLUS
(4) Doerfler, W; Prog Nucleic Acid Res Mol Biol 1993, V46, P1 CAPLUS
(5) Feng, M; Nat Biotechnol 1997, V15, P866 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 7 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:398705 CAPLUS
DOCUMENT NUMBER: 131:165951
TITLE: Isolation of recombinant **adeno-associated virus** vector-cellular DNA junctions from mouse liver
AUTHOR(S): Nakai, Hiroyuki; Iwaki, Yuichi; Kay, Mark A.; Couto, Linda B.
CORPORATE SOURCE: Avigen Inc., Alameda, CA, 94502, USA
SOURCE: J. Virol. (1999), 73(7), 5438-5447
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recombinant **adeno-assocd. virus** (**rAAV**) vectors allow for sustained expression of **transgene** products from mouse liver following a single portal vein administration. Here a **rAAV** vector expressing human coagulation factor IX (hF.IX), **AAV**-EF1.alpha.-F.IX (hF.IX expression was controlled by the human elongation factor 1.alpha. [EF1.alpha.] enhancer-**promoter**) was injected into mice via the portal vein or tail vein, or directly into the liver parenchyma, and the forms of **rAAV** vector DNA extd. from the liver were analyzed. Southern blot analyses suggested that **rAAV** vector integrated into the host genome, forming mainly head-to-tail concatemers with occasional deletions of the **inverted terminal repeats** (**ITRs**) and their flanking sequences. To further confirm vector integration, we developed a shuttle vector system and isolated and sequenced **rAAV** vector-cellular DNA junctions from transduced mouse livers. Anal. of 18 junctions revealed various rearrangements, including **ITR** deletions and amplifications of the vector and cellular DNA sequences. The breakpoints of the vector were mostly located within the **ITRs**, and cellular DNA sequences were recombined with the vector genome in a nonhomologous manner. Two **rAAV**-targeted DNA sequences were identified as the mouse rRNA gene and the .alpha.1 collagen gene. These observations serve as direct evidence of **rAAV** integration into the host genome of mouse liver and allow us to begin to elucidate the mechanisms involved in **rAAV** integration into tissues in vivo.

REFERENCE COUNT: 39
REFERENCE(S):
(1) Allen, J; J Virol 1997, V71, P6816 CAPLUS
(2) Balague, C; J Virol 1997, V71, P3299 CAPLUS
(3) Cheung, A; J Virol 1980, V33, P739 CAPLUS
(4) Clark, K; Hum Gene Ther 1997, V8, P659 CAPLUS
(6) Duan, D; J Virol 1998, V72, P8568 CAPLUS

Searcher : Shears 308-4994

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 8 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:181479 CAPLUS
DOCUMENT NUMBER: 130:333447
TITLE: Development of animal models for **adeno-associated virus** site-specific integration
AUTHOR(S): Rizzuto, Gabriella; Gorgoni, Barbara; Cappelletti, Manuela; Lazzaro, Domenico; Gloaguen, Isabelle; Poli, Valeria; Sgura, Antonella; Cimini, Daniela; Ciliberto, Gennaro; Cortese, Riccardo; Fattori, Elena; La Monica, Nicola
CORPORATE SOURCE: IRBM, Pomezia, 00040, Italy
SOURCE: J. Virol. (1999), 73(3), 2517-2526
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **adeno-assocd. virus** (**AAV**) is unique in its ability to target viral DNA integration to a defined region of human chromosome 19 (AAVS1). Since AAVS1 sequences are not conserved in a rodent's genome, no animal model is currently available to study **AAV**-mediated site-specific integration. We describe here the generation of transgenic rats and mice that carry the AAVS1 3.5-kb DNA fragment. To test the response of the transgenic animals to Rep-mediated targeting, primary cultures of mouse fibroblasts, rat hepatocytes, and fibroblasts were infected with wild-type **AAV**. PCR amplification of the **inverted terminal repeat** (**ITR**)-AAVS1 junction revealed that the **AAV** genome integrated into the AAVS1 site in fibroblasts and hepatocytes. Integration in rat fibroblasts was also obsd. upon transfection of a plasmid contg. the rep gene under the control of the p5 and p19 **promoters** and a dicistronic cassette carrying the green fluorescent protein (GFP) and neomycin (neo) resistance gene between the **ITRs** of **AAV**. The localization of the GFP-Neo sequence in the AAVS1 region was detd. by Southern blot and FISH anal. Lastly, **AAV** genomic DNA integration into the AAVS1 site in vivo was assessed by virus injection into the quadriceps muscle of transgenic rats and mice. Rep-mediated targeting to the AAVS1 site was detected in several injected animals. These results indicate that the transgenic lines are proficient for Rep-mediated targeting. These animals should allow further characterization of the mol. aspects of site-specific integration and testing of the efficacy of targeted integration of **AAV** recombinant vectors designed for human gene therapy.

REFERENCE COUNT: 52

REFERENCE(S): (1) Balague, C; J Virol 1997, V71, P3299 CAPLUS
(2) Bartlett, J; Gene therapy protocols 1997, P25 CAPLUS
(4) Berry, M; J Cell Biol 1969, V43, P506 CAPLUS
(5) Boussif, O; Gene Ther 1996, V3, P1074 CAPLUS
(6) Cheung, A; J Virol 1980, V33, P739 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 9 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:125734 CAPLUS
DOCUMENT NUMBER: 130:178345
TITLE: Hybrid adenovirus-**adeno-associated virus** and its use in cell transformation
INVENTOR(S): Wilson, James M.; Kelley, William M.; Fisher, Krishna J.
PATENT ASSIGNEE(S): The Trustees of the University of Pennsylvania, USA
SOURCE: U.S., 45 pp., Cont.-in-part of U.S. Ser. No. 331,384.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5871982	A	19990216	US 1997-836087	19970825
US 5856152	A	19990105	US 1994-331384	19941028
WO 9613598	A2	19960509	WO 1995-US14018	19951027
WO 9613598	A3	19960815		
W: AL, AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
EP 1046711	A2	20001025	EP 2000-103600	19951027
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				

PRIORITY APPLN. INFO.: US 1994-331384 19941028
WO 1995-US14018 19951027
EP 1995-942840 19951027

AB The present invention provides a hybrid vector construct which comprises a portion of an adenovirus, 5' and 3' **inverted terminal repeat** (**ITR**) sequences from an **adeno-assocd. virus** (**AAV**), and

a selected **transgene**. Also provided is a hybrid virus linked via a polycation conjugate to an **AAV** rep gene to form a single particle. These trans-infection particles are characterized by high titer **transgene** delivery to a host cell and the ability to stably integrate the **transgene** into the host cell chromosome. Also disclosed is the use of the hybrid vectors and viruses to produce large quantities of recombinant **AAV**. Hybrid adeno-**adeno-assocd. virus** Ad.AV.CMVLacZ was prepd. as well as a complex of polylysine with this hybrid virus and plasmid pRep78/52 (providing the **adeno-assocd. virus** rep gene). HeLa cells were infected with the complex and the lacZ gene was found to be integrated into the cell genome.

REFERENCE COUNT: 46
REFERENCE(S):
(1) Anon; WO 9118088 1991 CAPLUS
(2) Anon; WO 9324641 1993 CAPLUS
(3) Anon; WO 9412649 1994 CAPLUS
(4) Anon; WO 9413788 1994 CAPLUS
(5) Anon; WO 9417832 1994 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 10 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:795152 CAPLUS
DOCUMENT NUMBER: 130:33988
TITLE: replication-defective, packaging-attenuated mini-adenoviral vector containing minimal cis-element and use for factor VIII gene therapy of hemophilia
INVENTOR(S): Zhang, Wei-wei; Alemany, Ramon; Dai, Yifan; Josephs, Steven; Balague, Cristina; Ayares, David; Schneiderman, Richard
PATENT ASSIGNEE(S): Baxter International Inc., USA
SOURCE: PCT Int. Appl., 185 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9854345	A1	19981203	WO 1998-US10330	19980519

W: CA, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRIORITY APPLN. INFO.: US 1997-866403 19970530

AB Claimed are Ad vectors that carry the minimal cis-element of the Ad genome (mini-Ad vector) and are capable of delivering **transgenes** and/or heterologous DNA up to 36 kb, and use for

treatment of hemophilia in humans by transfection with a factor VIII cDNA. This invention is related to adenoviral (Ad) vectors and their applications in the field of genetic medicine, including gene transfer, gene therapy, and gene vaccination. The generation and propagation of the mini-Ad vectors requires trans-complementation of a packaging-attenuated and replication-defective helper Ad (helper) in an Ad helper cell line. This invention further comprises a methodol. for generating a mini-adenoviral (mini-Ad) vector for use in gene therapy of hemophilia and animal test systems for in vivo evaluation of the Ad vectors. More specifically, this invention describes factor VIII(FVIII) Ad vectors that only contain minimal cis-element of the Ad genome (so-called mini-Ad) and comprise a human FVIII cDNA with other supporting DNA elements up to 36 kb. The FVIII mini-Ad can be generated and preferentially amplified through the assistance of a packaging-attenuated helper Ad and a helper cell line. This invention also reports designs and methods for producing transgenic mouse models that can be used for in vivo testing the mini-Ad.

REFERENCE COUNT: 14
REFERENCE(S):
(1) American Cyanamid Company; EP 0592836 A 1994
(2) Baxter International Inc; WO 9745550 A 1997
(8) Grable; Journal of Virology 1992, V66(2), P723 CAPLUS
(9) Ikawa; FEBS Letters 1995, V375(1,2), P125 CAPLUS
(10) Martin; US 5470560 A 1995 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 11 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:682550 CAPLUS
DOCUMENT NUMBER: 129:286758
TITLE: Recombinant vectors with improved packaging capacity derived from **adeno-associated virus** and their use in gene therapy
INVENTOR(S): Ciliberto, Gennaro; Colloca, Stefano; Fattori, Elena; Fipaldini, Cristina; La, Monica Nicola; Monciotti, Andrea; Palombo, Fabio; Pieroni, Luisa; Recchia, Alessandra; Rizzuto, Gabriella
PATENT ASSIGNEE(S): Istituto Di Ricerche Di Biologia Molecolare P. Angeletti S.P.A., Italy; La Monica, Nicola; et al.
SOURCE: PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9845462	A1	19981015	WO 1998-IT82	19980408
W: AU, CA, CN, IL, JP, KR, MX, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9870778	A1	19981030	AU 1998-70778	19980408
WO 9953084	A1	19991021	WO 1999-EP2384	19990408
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9939265	A1	19991101	AU 1999-39265	19990408
PRIORITY APPLN. INFO.:			IT 1997-RM200	19970408
			WO 1998-IT82	19980408
			GB 1998-13670	19980624
			WO 1999-EP2384	19990408

AB The present invention refers to vectors derived form recombinant **Adeno-assocd. virus** (AVV) which comprise at least one selected **transgene** between the sequences of the 5' and 3' **inverted terminal repeats** (**ITRs**) from **AAV**, and a DNA sequence encoding one or more **AAV** Rep protein, or a fragment or a deriv. thereof, outside of the context of the **AAV ITRs**. These vectors have a larger packaging capacity and prior art vectors. The vectors according to the invention are useful in gene therapy. Thus, plasmid pITR(GFP-Neo)P5Rep was prepd. and HeLa cells were transfected with it. This plasmid contains the GFP gene under control of the CMV early **promoter** and the neomycin resistance gene under control of the SV40 early **promoter** between the 3'- and 5'-**ITRs** and the Rep gene controlled by the P5 and P19 **promoters** outside of the **ITRs**. The **ITR**-flanked expression construct was inserted into the HeLa cell genome in a Rep-dependent manner at the aavs1 site.

L20 ANSWER 12 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:479614 CAPLUS
DOCUMENT NUMBER: 129:91396
TITLE: Microinjection of **transgene** into mammalian cells, improvement of chromosomal integration of **transgene**, and use for gene therapy
INVENTOR(S): Davis, Brian; Yao, Aqoing
PATENT ASSIGNEE(S): Gene-Cell, USA

SOURCE: PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9828417	A1	19980702	WO 1997-US24236	19971220
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9858121	A1	19980717	AU 1998-58121	19971220
EP 946718	A1	19991006	EP 1997-954318	19971220
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRIORITY APPLN. INFO.:			US 1996-33816	19961223
			WO 1997-US24236	19971220

AB Disclosed is a method for introducing a **transgene** construct into a recipient mammalian cell with improved chromosomal integration of the **transgene** and thus, the transformation efficiency. The method uses a compn. comprised of a **transgene** construct contg. an encoding DNA sequence flanked by a retroviral (e.g. M-MuLV and HIV-1) LTR (long terminal repeat) and a retroviral integrase protein that facilitates the chromosomal integration. Alternatively, it uses a compn. comprised of an encoding DNA sequence flanked by **AAV** (**adeno-assocd. virus**) **ITR** (**inverted terminal repeat**) and the **AAV** integration enzyme Rep78. Also disclosed is a microinjection method, where the target cells may be grown in a non-adherent state or immobilized onto a substrate surface coated with an adherent mol., e.g., fibronectin. Microinjection of a **transgene** construct that express both the red shifted Green Fluorescent Protein (rsGFP) reporter gene and the human O6-methylguanine DNA methyltransferase (MGMT) gene into CD34+ human hematopoietic stem cells, and its application in gene therapy are also described.

L20 ANSWER 13 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:303188 CAPLUS
DOCUMENT NUMBER: 129:77198
TITLE: Site-specific integration in mammalian cells mediated by a new hybrid baculovirus-

adeno-associated virus
vector

AUTHOR(S): Palombo, Fabio; Monciotti, Andrea; Recchia, Alessandra; Cortese, Riccardo; Ciliberto, Gennaro; La Monica, Nicola
CORPORATE SOURCE: IRBM P. Angeletti, Pomezia, 00040, Italy
SOURCE: J. Virol. (1998), 72(6), 5025-5034
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Baculovirus can transiently transduce primary human and rat hepatocytes, as well as a subset of stable cell lines. To prolong **transgene** expression, we have developed new hybrid vectors which assoc. key elements from **adeno-assocd. virus** (**AAV**) with the elevated transducing capacity of baculovirus. The hybrid vectors contain a **transgene** cassette composed of the .beta.-galactosidase (.beta.-Gal) reporter gene and the hygromycin resistance (Hygr) gene flanked by the **AAV inverted terminal repeats** (**ITRs**), which are necessary for **AAV** replication and integration in the host genome. Constructs were derived both with and without the **AAV** rep gene under the p5 and p19 **promoters** cloned in different positions with respect to the baculovirus polyhedrin **promoter**. A high-titer prepn. of baculovirus-**AAV** (Bac-**AAV**) chimeric virus contg. the **ITR**-Hygr-.beta.-Gal sequence was obtained with insect cells only when the rep gene was placed in an antisense orientation to the polyhedrin **promoter**. Infection of 293 cells with Bac-**AAV** virus expressing the rep gene results in a 10-to 50-fold increase in the no. of Hygr stable cell clones. Addnl., rep expression detd. the localization of the **transgene** cassette in the aavs1 site in approx. 41% of cases as detected by both Southern blotting and fluorescent in situ hybridization anal. Moreover, site-specific integration of the **ITR**-flanked DNA was also detected by PCR amplification of the **ITR**-aavs1 junction in transduced human fibro-blasts. These data indicate that Bac-**AAV** hybrid vectors can allow permanent, nontoxic gene delivery of DNA constructs for ex vivo treatment of primary human cells.

L20 ANSWER 14 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:181689 CAPLUS
DOCUMENT NUMBER: 128:290832
TITLE: Viral sequences enable efficient and tissue-specific expression of **transgenes** in Xenopus
AUTHOR(S): Fu, Yuchang; Wang, Yibin; Evans, Sylvia M.
CORPORATE SOURCE: Dep. Med., Univ. California, San Diego, CA,

92093-0613, USA
SOURCE: Nat. Biotechnol. (1998), 16(3), 253-257
CODEN: NABIF9; ISSN: 1087-0156
PUBLISHER: Nature America
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Expression of **transgenes** within a single generation by direct DNA injection into vertebrate embryos has been plagued by inefficient and nonuniform gene expression. We report a novel strategy for efficient and stable expression of **transgenes** driven by both ubiquitous and tissue-specific **promoters** by direct DNA injection into developing Xenopus laevis embryos. This strategy involves flanking expression cassettes of interest with **inverted terminal repeat** sequences (**ITRs**) from **adeno-assocd. virus** . Our results suggest that the **ITR** strategy may be generally applicable to other systems, such as zebra fish and embryonic stem cells, and may enable tissue-specific expression of **transgenes** in problematic contexts.

L20 ANSWER 15 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:805844 CAPLUS
DOCUMENT NUMBER: 128:58279
TITLE: Mini-adenoviral vector having reduced immunological responses for preparation of transgenic animals and gene therapy
INVENTOR(S): Zhang, Wei-Wei; Alemany, Ramon; Dai, Yifan; Josephs, Steven; Balague, Cristina; Ayares, David; Schneiderman, Richard
PATENT ASSIGNEE(S): Baxter International Inc., USA; Zhang, Wei-Wei; Alemany, Ramon; Dai, Yifan; Josephs, Steven; Balague, Cristina; Ayares, David; Schneiderman, Richard
SOURCE: PCT Int. Appl., 192 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9745550	A2	19971204	WO 1997-US10218	19970530
WO 9745550	A3	19980409		
W: CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 954591	A2	19991110	EP 1997-928961	19970530
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC,				

PT, IE, FI
PRIORITY APPLN. INFO.: US 1996-658961 19960531
US 1997-791218 19970131
WO 1997-US10218 19970530

AB Mini-adenoviral (Ad) vectors that have reduced immunol. responses in host animals, that are able to integrated into the host genomes, and that are able to maintain episomal replication of the **transgene** are prepd. for gene transfer, gene therapy, and gene vaccination. The min-Ad vectors that carry the minimal cis-element of the Ad genome are capable of delivering **transgenes** and/or heterologous DNA up to 36 kb. The generation and propagation of the mini-Ad vectors require trans-complementation of a packaging-attenuated and replication-defective helper Ad (helper) in an Ad helper cell line. This invention further comprises a methodol. for generating a mini-adenoviral (mini-Ad) vector for use in gene therapy of hemophilia and animal test systems for in vivo evaluation of the Ad vectors. Also reported are designs and methods for producing transgenic mouse models that can be used for in vivo testing the mini-Ad.

L20 ANSWER 16 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:166452 CAPLUS
DOCUMENT NUMBER: 126:247299
TITLE: HSV/**AAV** hybrid amplicon vectors extend **transgene** expression in human glioma cells
AUTHOR(S): Johnston, Karen M.; Jacoby, David; Pechan, Peter A.; Fraefel, Cornel; Borghesani, Paul; Schuback, Deborah; Dunn, Robert J.; Smith, Frances I.; Breakefield, Xandra O.
CORPORATE SOURCE: Massachusetts General Hospital, Harvard Medical School, Boston, MA, 02114, USA
SOURCE: Hum. Gene Ther. (1997), 8(3), 359-370
CODEN: HGTHE3; ISSN: 1043-0342
PUBLISHER: Liebert
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Novel hybrid vectors, which incorporate crit. elements of both herpes simplex virus type 1 (HSV)-1 amplicon vectors and **adeno-assocd. virus** (**AAV**) vectors, are able to sustain **transgene** expression in dividing glioma cells for over 2 wk. These vectors combine the high infectability and large **transgene** capacity of HSV-1 vectors with the potential for episomal amplification and chromosomal integration of **AAV** vectors. The hybrid vectors contain the HSV-1 origin of DNA replication, oriS, and the DNA cleavage/packaging signal, pac, which allow amplicon replication and packaging in HSV-1 virions. The lacZ reporter gene under

control of the CMV IE1 **promoter** is flanked by **AAV** **inverted terminal repeat** (**ITR**) sequences, which facilitate replication and genomic integration of this cassette in the host cell nucleus. Constructs were generated with or without the **AAV** rep gene (rep+ and rep-) to assess its importance in extending **transgene** expression. Expression of Rep proteins was confirmed by Western blot anal. An HSV-1 amplicon construct contg. the reporter gene, but no **AAV** sequences, was used as a control. Constructs were packaged into HSV-1 virions with or without helper virus and these vector stocks were used to infect human U87 glioma cells in culture. The hybrid vectors supported **transgene** retention and expression for over 2 wk, whereas the control amplicon vector lost the **transgene** after 10 days. Expression was somewhat longer for the rep+ as compared to the rep- hybrid vectors. Toxicity due to the HSV-1 helper virus was eliminated using helper virus-free amplicon vector stocks. **Transgene** constructs could also be packaged in **AAV** virions, using **AAV** and adenovirus or HSV-1 helper functions. These HSV/**AAV** hybrid vectors should allow long-term, nontoxic gene delivery of DNA constructs to both dividing and nondividing cells.

L20 ANSWER 17 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:428704 CAPLUS
DOCUMENT NUMBER: 125:78521
TITLE: Lipid vesicles containing **adeno-associated virus** rep protein for **transgene** integration and gene therapy
INVENTOR(S): Wiener, Stephen M.; Chiorini, John A.; Safer, Brian; Kotin, Robert M.
PATENT ASSIGNEE(S): United States Dept. of Health and Human Services, USA
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9615777	A1	19960530	WO 1995-US13190	19951116
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2205874	AA	19960530	CA 1995-2205874	19951116
EP 786989	A1	19970806	EP 1995-943565	19951116
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL,				

PT, SE
JP 10509046 T2 19980908 JP 1995-516836 19951116
PRIORITY APPLN. INFO.: US 1994-344729 19941123
WO 1995-US13190 19951116

AB A compn. for delivering at least one DNA sequence encoding a desired portion or polypeptide (such as a therapeutic agent) to a cell is claimed. The compn. comprises an **adeno-assocd. virus** rep protein (or a nucleic acid sequence encoding an **adeno-assocd. virus** rep protein) and a genetic construct including at least one DNA sequence encoding a protein or polypeptide or genetic transcript of interest and a **promoter** controlling the at least one DNA sequence. The genetic construct also includes a first **adeno-assocd. virus ITR** or portion or deriv. thereof and a second **adeno-assocd. virus ITR** or a portion or deriv. thereof. The first and second **adeno-assocd. virus ITRs** or portions or derivs. thereof flank the at least one DNA sequence encoding the protein or polypeptide or genetic transcript of interest and the **promoter** controlling the at least one DNA sequence encoding the protein or polypeptide or genetic transcript of interest. Such a compn. provides for integration of genetic material at a specific locus in the human chromosome, while minimizing the possibility of inadvertent inactivation of host genes and minimizing the possibility of viral contamination. Plasmid pAAVRSVF9, contg. a Rous sarcoma virus **promoter** fused to the human factor IX gene flanked by **adeno-assocd. virus** 5'- and 3'-**ITR**'s, was constructed. Liposomes contg. this plasmid and **adeno-assocd. virus** Rep78 protein were prepd. for use in treatment of hemophilia B.

L20 ANSWER 18 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:428562 CAPLUS
DOCUMENT NUMBER: 125:78506
TITLE: Hybrid adenovirus-**adeno-associated virus** and its use in cell transformation
INVENTOR(S): Wilson, James M.; Kelley, William M.; Fisher, Krishna J.
PATENT ASSIGNEE(S): Trustees of the University of Pennsylvania, USA
SOURCE: PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9613598	A2	19960509	WO 1995-US14018	19951027
WO 9613598	A3	19960815		
W: AL, AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5856152	A	19990105	US 1994-331384	19941028
CA 2203808	AA	19960509	CA 1995-2203808	19951027
AU 9644055	A1	19960523	AU 1996-44055	19951027
AU 695811	B2	19980820		
EP 797678	A2	19971001	EP 1995-942840	19951027
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV				
JP 10507928	T2	19980804	JP 1995-514801	19951027
EP 1046711	A2	20001025	EP 2000-103600	19951027
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
US 5871982	A	19990216	US 1997-836087	19970825
PRIORITY APPLN. INFO.:			US 1994-331384	19941028
			EP 1995-942840	19951027
			WO 1995-US14018	19951027

AB The present invention provides a hybrid vector construct which comprises a portion of an adenovirus, 5' and ' **ITR** sequences from an **AAV**, and a selected **transgene**. Also provided is a hybrid virus linked via a polycation conjugate to an **AAV** rep gene to form a single particle. These trans-infection particles are characterized by high titer **transgene** delivery to a host cell and the ability to stably integrate the **transgene** into the host cell chromosome. Also disclosed is the use of the hybrid vectors and viruses to produce large quantities of recombinant **AAV**. Hybrid adeno-**adeno-assocd. virus** Ad.AV.CMVLacZ was prepd. as well as a complex of polylysine with this hybrid virus and plasmid pRep78/52 (providing the **adeno -assocd. virus** rep gene). HeLa cells were infected with the complex and the lacZ gene was found to be integrated into the cell genome.

L20 ANSWER 19 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:353786 CAPLUS
DOCUMENT NUMBER: 125:1163
TITLE: Comparison of **promoter** strengths on gene delivery into mammalian brain cells using **AAV** vectors
AUTHOR(S): Doll, R. F.; Crandall, J. E.; Dyer, C. A.;

Aucoin, J. M.; Smith, F. I.
CORPORATE SOURCE: EK Shriver Center, Waltham, MA, USA
SOURCE: Gene Ther. (1996), 3(5), 437-447
CODEN: GETHEC; ISSN: 0969-7128
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Recent reports have suggested that delivery of genes flanked by **adeno-assocd. virus (AAV) ITRs** may be useful for gene therapy of diseases that involve the brain. We have compared the efficiency of gene expression in vitro in CNS-derived cells from four different **promoters** when the **transgene** is flanked by **AAV ITRs**, using both transfection via cationic liposomes, and infection via **rAAV**. The human cytomegalovirus (CMV) immediate-early enhancer/**promoter**, the SV40 early enhancer/**promoter**, the JC polyomavirus **promoter**, and the chicken .beta.-actin **promoter** coupled to the CMV enhancer were able to drive expression of the reporter gene .beta.-galactosidase in all tumor and primary brain cell cultures tested. Although the relative order of efficiency differed between cell types, the CMV **promoter** was always the strongest, generally by at least one order of magnitude. A comparison of the relative levels of expression seen between different cell types on transfection and infection suggest that not all CNS-derived cells are infected equally efficiently by **rAAvs**. High levels of expression were seen within 24 h of **transgene** delivery by either transfection or infection, dropping dramatically within days. All cell types and **promoters** showed the same decline, suggesting that transient expression by rep **rAAVs** may be efficient, but stable expression as detected in this system is a low frequency event. In vivo studies using the CMV **promoter** also suggest that although rep- **rAAVs** are able to infect efficiently CNS cells and produce high levels of gene expression shortly after transduction, the majority of such infections do not lead to stable high-level expression of **transgenes**.

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 16:07:37 ON 01 DEC 2000)
L21 36 S L19
L22 28 S L21 NOT L8
L23 12 DUP REM L22 (16 DUPLICATES REMOVED)

L23 ANSWER 1 OF 12 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-271457 [23] WPIDS
DOC. NO. CPI: C2000-082949
TITLE: Human type-5 recombinant adenovirus vector used for targeted gene therapy for heart disease and evaluating gene function contains a tissue-restricted **promoter** and

inverted terminal repeat
sequences.

DERWENT CLASS: B04 D16
INVENTOR(S): CHIEN, K R; EVANS, S; WANG, Y
PATENT ASSIGNEE(S): (REGC) UNIV CALIFORNIA
COUNTRY COUNT: 87
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000015821	A1	20000323	(200023)*	EN	33

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW

AU 9958195	A	20000403	(200034)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000015821	A1	WO 1999-US20730	19990910
AU 9958195	A	AU 1999-58195	19990910

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9958195	A	Based on	WO 200015821

PRIORITY APPLN. INFO: US 1998-99960 19980911
AN 2000-271457 [23] WPIDS
AB WO 200015821 A UPAB: 20000516
NOVELTY - Human type-5 recombinant adenovirus vector (I) with tissue specific transcription of a **transgene** comprises a tissue-restricted **promoter** and **inverted terminal repeat** (ITR) sequences from human **adeno-associated virus** (AVV).
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) a method for targeted gene therapy for heart disease comprising combining a cardiac-restricted cellular **promoter** with **ITR** sequences from **adeno-associated virus**; and
(2) a method for the evaluation of gene function comprising combining a cardiac-restricted cellular **promoter** with **ITR** sequences from **adeno-associated**

virus.

ACTIVITY - Cardiant.

No biological data.

MECHANISM OF ACTION - Gene therapy.

USE - (I) is used for targeted gene therapy for heart disease and for evaluating gene function (claimed). Cardiac restricted transcription of a **transgene** in both neonatal and mature cardiac tissues can be achieved to treat inherited and acquired heart diseases.

ADVANTAGE - The vector is suitable for tissue specific use in vivo and in vitro and provides cardiac restricted transcription.

Dwg.0/2

L23 ANSWER 2 OF 12 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD

ACCESSION NUMBER: 2000-062462 [05] WPIDS

DOC. NO. NON-CPI: N2000-048899

DOC. NO. CPI: C2000-017348

TITLE: Recombinant **adeno-associated virus** vector useful for gene therapy against disorders related to blood, neurological and muscular systems.

DERWENT CLASS: B04 D16 P14

INVENTOR(S): DUAN, D; ENGELHARDT, J F

PATENT ASSIGNEE(S): (DUAN-I) DUAN D; (ENGE-I) ENGELHARDT J F; (IOWA) UNIV IOWA RES FOUND

COUNTRY COUNT: 86

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9960146	A1	19991125	(200005)*	EN	121
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW					
AU 9940912	A	19991206	(200019)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9960146	A1	WO 1999-US11197	19990520
AU 9940912	A	AU 1999-40912	19990520

FILING DETAILS:

PATENT NO	KIND	PATENT NO

Searcher : Shears 308-4994

AU 9940912 A Based on WO 9960146

PRIORITY APPLN. INFO: US 1999-276625 19990325; US 1998-86166 19980520

AN 2000-062462 [05] WPIDS

AB WO 9960146 A UPAB: 20000128

NOVELTY - New isolated and purified DNA molecule comprises DNA segment (I) (biologically active subunit of variant) of circular intermediate of **adenoassociated virus** (**AAV**) that confers increased episomal stability, persistence or abundance in host cell.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a gene transfer vector (V) comprising (I) and a second DNA segment comprising a gene;

(2) delivering a gene into a host cell by contacting the host cell with (V);

(3) a host cell comprising (V);

(4) a host cell comprising DNA molecule with (I);

(5) animal comprising (V);

(6) expressing a gene in eukaryotic cell by transfecting susceptible eukaryotic host cell with (V) and recombinant adenovirus helper vector to form packaged viral particles and infecting the eukaryotic host cell with packaged viral particles;

(7) a composition (C) comprising two (**AAV**) vectors, (**AAV**-1 and **AAV**- 2) comprising 5' **inverted terminal repeats** (**ITR**) of (**AAV**) and 3' (**ITR**) with **AAV**-1 comprising splice donor site and a portion of open reading frame (ORF)-(a) operably linked to a **promoter** while **AAV**-2 comprising splice acceptor site and (ORF) which together with (ORF)-(a) forms a full length polypeptide; and

(8) transferring and expressing a polypeptide in a host cell by contacting host cell with (C).

ACTIVITY - Antisickling; hemostatic; neuroprotective; antiparkinsonian.

MECHANISM OF ACTION - Gene therapy.

USE - Composition containing a vector with therapeutic gene and delivery vehicle or containing two vectors expressing a full length polypeptide coordinatedly is useful for manufacturing a medicament for treating pathological condition or symptom in a mammal (claimed) (V) is useful for therapeutic or prophylactic treatments of blood disorders (e.g. sickle cell anemia, thalassemias, hemophilias and Fanconi's anemias), neurological disorders (e.g Alzheimer's disease, Parkinson's disease) and muscle disorders.

ADVANTAGE - (**AAV**) can infect non-dividing cells effectively. All (**AAV**) genes are eliminated in the vector and are safer than Ad vectors. Integration of **AAV** into

host chromosome is maintained with increased episomal stability. (**AAV**) is extremely stable with resistance to detergents, pH changes and heat (even upto 56 deg. C for more than one hour). Lyophilisation and solubilization is effective without loss of activity. This is also useful to overcome size limitation for **transgenes** within **rAAV** vectors and allows incorporation of larger transcriptional regulatory regions.

DESCRIPTION OF DRAWING(S) - The figure shows the application of **rAAV** circular concatamers to deliver trans-splicing vectors with large gene inserts.

Dwg.19/19

L23 ANSWER 3 OF 12 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1999-347721 [29] WPIDS
DOC. NO. CPI: C1999-102401
TITLE: Fusion of altered adeno-associated Rep protein and hormone binding site.
DERWENT CLASS: B04 D16
INVENTOR(S): CILIBERTO, G; RINAUDO, C; TONIATTI, C
PATENT ASSIGNEE(S): (RICE-N) IST RICERCHE BIOL MOLECOLARE ANGELETTI
COUNTRY COUNT: 30
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9927110	A1	19990603	(199929)*	EN	64
RW: AT BE CH CY DE DK EA ES FI FR GB GR IE IT LU MC NL PT SE					
W: AU CA CN IL JP KR MX NO NZ US					
AU 9912596	A	19990615	(199944)		
EP 1032678	A1	20000906	(200044)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9927110	A1	WO 1998-IT329	19981120
AU 9912596	A	AU 1999-12596	19981120
EP 1032678	A1	EP 1998-955912	19981120
		WO 1998-IT329	19981120

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9912596	A	Based on	WO 9927110
EP 1032678	A1	Based on	WO 9927110

PRIORITY APPLN. INFO: IT 1997-RM724 19971121

Searcher : Shears 308-4994

AN 1999-347721 [29] WPIDS
AB WO 9927110 A UPAB: 19990723
NOVELTY - A fusion protein (I) of:
(i) a mutein of **adeno-associated virus** (**AAV**) Rep 78 or Rep 68 protein, having at least one mutation in the region of amino acids (aa) 480-520 that (partly) inactivates the nuclear localization signal (NLS) and
(ii) the binding domain (BD) for a steroid hormone.
Optionally (i) includes the wild-type region from aa 521 to the C-terminus.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) mutein (II) of Rep 78 or 68 with at last one mutation in the 480-520 region, optionally including the wild-type region from aa 521 to the C-terminus;
(2) DNA (III) encoding (I) or (II);
(3) vector containing (III); and
(4) method for regulating intracellular activity of Rep 78 or 68 by introducing into a cell either (I) or DNA encoding it, then treatment of the cell with a steroid hormone or its analog.
ACTIVITY - None given.
MECHANISM OF ACTION - Mutational deletion of the NLS and fusion to a steroid BD, makes site-specific integration, at site aavs1 in chromosome 19, mediated by Rep proteins, dependent on hormonal regulation, i.e. (I) is inactive in absence of hormone but is quickly activated when this is added. Nucleic acid encoding a fusion (Rep1 Delta N/Pn) of Rep aas 1-491 and aas 679-891 of the human progesterone receptor was introduced into human kidney 293 cells and tested for ability to free fragments from plasmid DNA (encoding beta -galactosidase and hygromycin resistance) flanked by **AAV ITRs**, co-transfected into the cells. The encoded fusion protein had low basal activity but this was much increased in presence of 1 micro M of the progesterone antagonist RU486. The fusion was also active for site-specific integration, but in this case RU486 was essential for activity.
USE - (I) is used, in conjunction with vectors containing a therapeutic **transgene** and flanked by **AAV inverted terminal repeats**, for somatic gene therapy.
ADVANTAGE - Integration into a specific site prolongs expression of the transferred **transgene** and reduces the risk of insertional mutagenesis.
Dwg.0/11

L23 ANSWER 4 OF 12 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1999-579915 [49] WPIDS
DOC. NO. CPI: C1999-168679
TITLE: Hybrid transgenic vectors useful for gene therapy.
DERWENT CLASS: B04 D16
Searcher : Shears 308-4994

INVENTOR(S): BREAKEFIELD, X O; JACOBY, D R; SMITH, F I
PATENT ASSIGNEE(S): (GEHO) GEN HOSPITAL CORP
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 5965441	A	19991012	(199949)*		22

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 5965441	A	Provisional	US 1996-30694	19961113
			US 1997-968434	19971112

PRIORITY APPLN. INFO: US 1996-30694 19961113; US 1997-968434 19971112
AN 1999-579915 [49] WPIDS
AB US 5965441 A UPAB: 19991124
NOVELTY - Hybrid gene vectors comprising a sequence of interest, herpesvirus (HSV) sequences, and **adeno-associated virus** (**AAV**) sequences, are new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) a hybrid vector comprising:

(i) a sequence of interest linked to a **promoter**;

(ii) a subset of sequences from HSV comprising an origin of replication and packaging signals; and

(iii) a subset of sequences from **AAV** comprising elements that increase the persistence of the vector in mitotic and non-mitotic cells;

(2) a hybrid vector for expressing a **transgene** comprising:

(i) an HSV derived sequence as in (1ii);

(ii) **inverted terminal repeat** sequences from **AAV** that flank a **transgene** cassette (which comprises a sequence as in (1i)); and optionally further comprising

(iii) an **AAV** rep gene inserted outside the **transgene** cassette; and

(3) methods for expressing a **transgene** as in (2) in a cell in vitro.

ACTIVITY - Anti-HIV; Nootropic; Neuroprotective; Antianemic; Cytostatic; Cardiant; Hepatotropic; Antidiabetic; Relaxant; Analgesic; Antiparkinsonian; Cerebroprotective.

MECHANISM OF ACTION - Gene therapy.

USE - The vectors can be used to deliver **transgenes**

to mitotic and postmitotic cells. The **transgene** can be used to treat inherited metabolic disorders (e.g. lysosomal storage disease and Lesch-Hyhan syndrome), inherited neurological diseases (e.g. amyloid polyneuropathy, Alzheimer's disease, Duchenne's muscular dystrophy, amyotrophic lateral sclerosis (ALS) and Parkinson's disease), blood disorders (e.g. sickle-cell anemia, clotting disorders and thalassemias), cystic fibrosis, diabetes, disorders of the lung and liver, heart and vascular disease, hormone deficiencies, movement disorders, pain, stroke, HIV, tumors, neoplasms, carcinomas, sarcomas, leukemias, lymphoma, astrocytomas, oligodendrogliomas, meningiomas, neurofibromas, ependymomas, Schwannomas, neurofibrosarcomas and glioblastomas.

Dividing HeLa and 293 cells (human immortalized cell lines) were infected with equal amounts (multiplicity of infection = 1) of hybrid vector and traditional HSV-1 amplicon vector. Cells were split 1:5 every 4 days and the proportion of cells expressing a fluorescent **transgene** was measured on a fluorescence activated cell sorter (FACS). The amplicon vector initially transduced greater than 85 % of total cells, however this fell to less than 3 % after 12 days. Hybrid transfected cells supported **transgene** expression for 30 days in 40 % of total dividing cells.

ADVANTAGE - The **transgene** can be maintained for extended periods (over 2 weeks) and combine the high infectability and large **transgene** capacity of HSV vectors with the potential for episomal amplification and chromosomal integration of **AAV** vectors.

DESCRIPTION OF DRAWING(S) - The diagram shows LacZ **transgene** bearing amplicon constructs.

Dwg.1/6

L23 ANSWER 5 OF 12 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 1999445839 MEDLINE
DOCUMENT NUMBER: 99445839
TITLE: Integrating adenovirus-**adeno-associated virus** hybrid vectors devoid of all viral genes.
AUTHOR: Lieber A; Steinwaerder D S; Carlson C A; Kay M A
CORPORATE SOURCE: Division of Medical Genetics, University of Washington, Seattle, Washington 98195, USA.
CONTRACT NUMBER: RO1 CA80192-01 (NCI)
RO1 DK49022 (NIDDK)
SOURCE: JOURNAL OF VIROLOGY, (1999 Nov) 73 (11) 9314-24.
Journal code: KCV. ISSN: 0022-538X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 200001

ENTRY WEEK: 20000104

AB Recently, we demonstrated that inverted repeat sequences inserted into first-generation adenovirus (Ad) vector genomes mediate precise genomic rearrangements resulting in vector genomes devoid of all viral genes that are efficiently packaged into functional Ad capsids. As a specific application of this finding, we generated adenovirus-**adeno-associated virus** (**AAV**) hybrid vectors, first-generation Ad vectors containing **AAV inverted terminal repeat** sequences (**ITRs**) flanking a reporter gene cassette inserted into the **E1** region. We hypothesized that the **AAV ITRs** present within the hybrid vector genome could mediate the formation of rearranged vector genomes (DeltaAd. **AAV**) and stimulate **transgene** integration. We demonstrate here that DeltaAd.**AAV** vectors are efficiently generated as by-products of first-generation adenovirus-**AAV** vector amplification. DeltaAd.**AAV** genomes contain only the **transgene** flanked by **AAV ITRs**, Ad packaging signals, and Ad **ITRs**. DeltaAd.**AAV** vectors can be produced at a high titer and purity. In vitro transduction properties of these deleted hybrid vectors were evaluated in direct comparison with first-generation Ad and recombinant **AAV** vectors (**rAAVs**). The DeltaAd. **AAV** hybrid vector stably transduced cultured cells with efficiencies comparable to **rAAV**. Since cells transduced with DeltaAd.**AAV** did not express cytotoxic viral proteins, hybrid viruses could be applied at very high multiplicities of infection to increase transduction rates. Southern analysis and pulsed-field gel electrophoresis suggested that DeltaAd.**AAV** integrated randomly as head-to-tail tandems into the host cell genome. The presence of two intact **AAV ITRs** was crucial for the production of hybrid vectors and for **transgene** integration. DeltaAd.**AAV** vectors, which are straightforward in their production, represent a promising tool for stable gene transfer in vitro and in vivo.

L23 ANSWER 6 OF 12 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1999292835 MEDLINE
DOCUMENT NUMBER: 99292835
TITLE: Isolation of recombinant **adeno-associated virus** vector-cellular DNA junctions from mouse liver.
AUTHOR: Nakai H; Iwaki Y; Kay M A; Couto L B
CORPORATE SOURCE: Avigen Inc., Alameda, California 94502, USA.. nakaih@leland.stanford.edu
CONTRACT NUMBER: HL53682 (NHLBI)
SOURCE: JOURNAL OF VIROLOGY, (1999 Jul) 73 (7) 5438-47. Journal code: KCV. ISSN: 0022-538X.
PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199909

AB Recombinant **adeno-associated virus** (**rAAV**) vectors allow for sustained expression of **transgene** products from mouse liver following a single portal vein administration. Here a **rAAV** vector expressing human coagulation factor F.IX (hF.IX), **AAV**-EF1alpha-F.IX (hF.IX expression was controlled by the human elongation factor 1alpha [EF1alpha] enhancer-**promoter**) was injected into mice via the portal vein or tail vein, or directly into the liver parenchyma, and the forms of **rAAV** vector DNA extracted from the liver were analyzed. Southern blot analyses suggested that **rAAV** vector integrated into the host genome, forming mainly head-to-tail concatemers with occasional deletions of the **inverted terminal repeats** (**ITRs**) and their flanking sequences. To further confirm vector integration, we developed a shuttle vector system and isolated and sequenced **rAAV** vector-cellular DNA junctions from transduced mouse livers. Analysis of 18 junctions revealed various rearrangements, including **ITR** deletions and amplifications of the vector and cellular DNA sequences. The breakpoints of the vector were mostly located within the **ITRs**, and cellular DNA sequences were recombined with the vector genome in a nonhomologous manner. Two **rAAV**-targeted DNA sequences were identified as the mouse rRNA gene and the alpha1 collagen gene. These observations serve as direct evidence of **rAAV** integration into the host genome of mouse liver and allow us to begin to elucidate the mechanisms involved in **rAAV** integration into tissues in vivo.

L23 ANSWER 7 OF 12 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1999-070221 [06] WPIDS
DOC. NO. NON-CPI: N1999-051382
DOC. NO. CPI: C1999-020755
TITLE: New Mini-Adenoviral Vector - contains minimal adenoviral cis-elements, useful for gene therapy, transfer or vaccination.
DERWENT CLASS: B04 D16 P14
INVENTOR(S): ALEMANY, R; AYARES, D; BALAGUE, C; DAI, Y; JOSEPHS, S; SCHNEIDERMAN, R; ZHANG, W
PATENT ASSIGNEE(S): (BAXT) BAXTER INT INC
COUNTRY COUNT: 20
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9854345	A1	19981203	(199906)*	EN	185

Searcher : Shears 308-4994

RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: CA JP

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9854345	A1	WO 1998-US10330	19980519

PRIORITY APPLN. INFO: US 1997-866403 19970530
AN 1999-070221 [06] WPIDS
AB WO 9854345 A UPAB: 19990316
New isolated DNA molecule (I) comprises: an adenoviral (Ad) **inverted terminal repeat** (**ITR**); a packaging signal; a transcriptional control region (TCR); an effector or reporter gene (II) and either a genomic integration sequence (GIS) or episomal maintenance sequence (EMS), all linked so as to generate an infectious, replication-defective recombinant Ad vector. The remainder of (I) does not encode any Ad proteins. Also claimed are: (1) isolated DNA (Ia), for generating an Ad vector as defined, comprising a (II) cassette flanked by adeno-associated (**AAV**) **ITR**; (2) isolated DNA (Ib), similar to (I) but including an **AAV-ITR** sequence and Rep expression cassette, but without GIS or EMS; (3) isolated DNA (Ic) comprising an **E1**-deleted helper Ad genome including an altered packaging signal so that the helper genome is packaged at lower frequency than the wild-type helper; (4) cells stably transfected with a DNA molecule (Id) containing the Ad **E1** gene having no sequence that overlaps the sequence of the **E1**-deleted helper; (5) recombinant Ad particle comprising (I); (6) generation of a non-human transgenic animal using a DNA molecule (Ie) containing the **AAV** S1 sequence and a drug-selection marker gene (DSMG); (7) non-human transgenic animal having the **AAV** S1 sequence stably integrated in its genome; (8) generating a transgenic animal tolerised to human factor VIII (hF8) or green fluorescent protein (GFP); (9) embryonic stem cells containing DNA molecule (If) comprising the hF8 gene under control of a liver-specific **promoter** and also including a DSMG; and (10) transgenic mice tolerised to hF8 or GFP.

USE - (I) is used, in conjunction with an Ad helper, to generate recombinant Ad vectors (A) for use in gene therapy (ex vivo or in vivo), transfer or vaccination, e.g. for treating cystic fibrosis or Duchenne muscular dystrophy (DMD); to induce anti-cancer immunity (by intratumour injection); to modify host immunity by genetic alteration of graft materials; for basic research and development; and for treating a wide range of liver diseases (following intravenous injection, most (A) becomes localised in the liver). (I), where (II) is the F8 gene, is used to treat

haemophilia. The transgenic animals are used for in vivo testing of the delivery of viral vectors that include an **AAV-ITR**, and the tolerised animals are used to evaluate expression of F8 and GFP (against which they do not generate an immune response).

ADVANTAGE - (A) contain the minimum cis-elements of the Ad genome and can accept up to 37 kb of transgenic or heterologous DNA. They are packaged more efficiently than the new helper viruses and the presence of GIS or EMS ensures long-term expression of the **transgene**, while retaining the tropism and host range of the helper virus. (A) can not produce replication-competent Ad and are less immunogenic than known vectors.

L23 ANSWER 8 OF 12 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1998241743 MEDLINE
DOCUMENT NUMBER: 98241743
TITLE: Site-specific integration in mammalian cells mediated by a new hybrid baculovirus-**adeno-associated virus** vector.
AUTHOR: Palombo F; Monciotti A; Recchia A; Cortese R; Ciliberto G; La Monica N
CORPORATE SOURCE: IRBM P. Angeletti, 00040 Pomezia, Italy.
SOURCE: JOURNAL OF VIROLOGY, (1998 Jun) 72 (6) 5025-34. Journal code: KCV. ISSN: 0022-538X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199807
ENTRY WEEK: 19980705

AB Baculovirus can transiently transduce primary human and rat hepatocytes, as well as a subset of stable cell lines. To prolong **transgene** expression, we have developed new hybrid vectors which associate key elements from **adeno-associated virus** (**AAV**) with the elevated transducing capacity of baculovirus. The hybrid vectors contain a **transgene** cassette composed of the beta-galactosidase (beta-Gal) reporter gene and the hygromycin resistance (Hygr) gene flanked by the **AAV inverted terminal repeats** (**ITRs**), which are necessary for **AAV** replication and integration in the host genome. Constructs were derived both with and without the **AAV** rep gene under the p5 and p19 **promoters** cloned in different positions with respect to the baculovirus polyheidrin **promoter**. A high-titer preparation of baculovirus-**AAV** (Bac-**AAV**) chimeric virus containing the **ITR**-Hygr-beta-Gal sequence was obtained with insect cells only when the rep gene was placed in an antisense orientation to the polyheidrin **promoter**. Infection of 293 cells with Bac-**AAV** virus expressing the rep gene results

in a 10- to 50-fold increase in the number of Hygr stable cell clones. Additionally, rep expression determined the localization of the **transgene** cassette in the aavs1 site in approximately 41% of cases as detected by both Southern blotting and fluorescent in situ hybridization analysis. Moreover, site-specific integration of the **ITR**-flanked DNA was also detected by PCR amplification of the **ITR**-aavs1 junction in transduced human fibroblasts. These data indicate that Bac-**AAV** hybrid vectors can allow permanent, nontoxic gene delivery of DNA constructs for ex vivo treatment of primary human cells.

L23 ANSWER 9 OF 12 SCISEARCH COPYRIGHT 2000 ISI (R)
ACCESSION NUMBER: 1999:11972 SCISEARCH
THE GENUINE ARTICLE: 148ND
TITLE: Reconstitution of NADPH oxidase activity in human X-linked chronic granulomatous disease myeloid cells after stable gene transfer using a recombinant **adeno-associated virus** 2 vector
AUTHOR: Li L L (Reprint); Dinauer M C
CORPORATE SOURCE: INDIANA UNIV, SCH MED, CANC RES INST, HERMAN B WELLS CTR PEDIAT RES, 1044 W WALNUT ST, ROOM 466, INDIANAPOLIS, IN 46202 (Reprint); INDIANA UNIV, SCH MED, JAMES WHITCOMB RILEY HOSP CHILDREN, DEPT PEDIAT HEMATOL ONCOL, INDIANAPOLIS, IN 46202; INDIANA UNIV, SCH MED, JAMES WHITCOMB RILEY HOSP CHILDREN, DEPT MED & MOL GENET, INDIANAPOLIS, IN 46202
COUNTRY OF AUTHOR: USA
SOURCE: BLOOD CELLS MOLECULES AND DISEASES, (15 DEC 1998) Vol. 24, No. 23, pp. 522-538.
Publisher: BLOOD CELLS FOUNDATION, C/O ERNEST BEUTLER SCRIPPS RES INST, DEPT MOLECULAR EXP MEDICINE, LA JOLLA, CA 92037.
ISSN: 1079-9796.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 70
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB X-linked chronic granulomatous disease (X-CGD) is an inherited disorder of host defense that results from mutations in the gene encoding gp91(phox), the large subunit of the phagocyte NADPH oxidase flavocytochrome b. In this study, we constructed a recombinant **adeno-associated virus**-2 (**AAV**) vector in which the constitutively active **promoter** from the human elongation factor-1a (EF-1a) gene drives expression of the murine gp91(phox) cDNA, and tested its ability to integrate and express in a human X-CGD myeloid cell line. The nitroblue tetrazolium (NBT) test of NADPH oxidase activity was

used to screen transduced cells for vector-mediated expression of recombinant gp91(phax). Between 2 - 14 % of cells were NET-positive in the first several weeks after transduction. Clones with NET-positive cells persisting several months after transduction had integrated vector by Southern blot analyses, with high level reconstitution of NADPH oxidase activity. In some clones, oxidase activity persisted for at least 8 to 14 months. In the majority, however, vector-derived RNA transcripts declined, although integrated **rAAV** genomes persisted. Decreased **transgene** expression was not directly correlated with methylation of the provirus. This study indicates that **rAAV** vectors can be successfully used for stable gene transfer, integration, and expression of recombinant gp91(phox) in a human myeloid cell line for at least 8 - 14 months in the absence of any selection. The EF-la promotor, however, was subject to silencing in a high percentage of clones with integrated **rAAV**, suggesting that alternative **promoters** may be desirable for achieving long-term expression in myeloid cells. (C) 1998 Academic Press.

L23 ANSWER 10 OF 12 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1998188425 MEDLINE
DOCUMENT NUMBER: 98188425
TITLE: Viral sequences enable efficient and tissue-specific expression of **transgenes** in Xenopus [published erratum appears in Nat Biotechnol 1998 Mar;16(3):253-7] [see comments].
COMMENT: Comment in: Nat Biotechnol 1998 Mar;16(3):233-4
AUTHOR: Fu Y; Wang Y; Evans S M
CORPORATE SOURCE: Department of Medicine, University of California, San Diego, La Jolla 92093-0613, USA.
SOURCE: NATURE BIOTECHNOLOGY, (1998 Mar) 16 (3) 253-7. Journal code: CQ3. ISSN: 1087-0156.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
AB Expression of **transgenes** within a single generation by direct DNA injection into vertebrate embryos has been plagued by inefficient and nonuniform gene expression. We report a novel strategy for efficient and stable expression of **transgenes** driven by both ubiquitous and tissue-specific **promoters** by direct DNA injection into developing Xenopus laevis embryos. This strategy involves flanking expression cassettes of interest with **inverted terminal repeat** sequences (**ITRs**) from **adeno-associated virus**. Our results suggest that the **ITR** strategy may be generally applicable to other systems, such as zebra fish and

embryonic stem cells, and may enable tissue-specific expression of **transgenes** in problematic contexts.

L23 ANSWER 11 OF 12 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 97200268 MEDLINE
DOCUMENT NUMBER: 97200268
TITLE: HSV/**AAV** hybrid amplicon vectors extend **transgene** expression in human glioma cells.
AUTHOR: Johnston K M; Jacoby D; Pechan P A; Fraefel C; Borghesani P; Schuback D; Dunn R J; Smith F I; Breakefield X O
CORPORATE SOURCE: Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston 02114, USA.
CONTRACT NUMBER: NS24279 (NINDS)
CA69246 (NCI)
DC002281 (NIDCD)
+
SOURCE: HUMAN GENE THERAPY, (1997 Feb 10) 8 (3) 359-70.
Journal code: A12. ISSN: 1043-0342.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199710
ENTRY WEEK: 19971004
AB Novel hybrid vectors, which incorporate critical elements of both herpes simplex virus type 1 (HSV-1) amplicon vectors and **adeno-associated virus** (**AAV**) vectors, are able to sustain **transgene** expression in dividing glioma cells for over 2 weeks. These vectors combine the high infectibility and large **transgene** capacity of HSV-1 vectors with the potential for episomal amplification and chromosomal integration of **AAV** vectors. The hybrid vectors contain the HSV-1 origin of DNA replication, oriS, and the DNA cleavage/packaging signal, pac, which allow amplicon replication and packaging in HSV-1 virions. The lacZ reporter gene under control of the CMV IE1 **promoter** is flanked by **AAV** **inverted terminal repeat** (**ITR**) sequences, which facilitate replication and genomic integration of this cassette in the host cell nucleus. Constructs were generated with or without the **AAV** rep gene (rep+ and rep-) to assess its importance in extending **transgene** expression. Expression of Rep proteins was confirmed by Western blot analysis. An HSV-1 amplicon construct containing the reporter gene, but no **AAV** sequences, was used as a control. Constructs were packaged into HSV-1 virions with or without helper virus and these vector stocks were used to infect human U87 glioma cells in culture. The hybrid vectors supported **transgene** retention and expression for over 2 weeks, whereas the control amplicon vector

lost the **transgene** after 10 days. Expression was somewhat longer for the rep+ as compared to the rep- hybrid vectors. Toxicity due to the HSV-1 helper virus was eliminated using helper virus-free amplicon vector stocks. **Transgene** constructs could also be packaged in **AAV** virions, using **AAV** and adenovirus or HSV-1 helper functions. These HSV/**AAV** hybrid vectors should allow long-term, nontoxic gene delivery of DNA constructs to both dividing and nondividing cells.

L23 ANSWER 12 OF 12 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 97013729 MEDLINE
DOCUMENT NUMBER: 97013729
TITLE: Comparison of **promoter** strengths on gene delivery into mammalian brain cells using **AAV** vectors.
AUTHOR: Doll R F; Crandall J E; Dyer C A; Aucoin J M; Smith F I
CORPORATE SOURCE: EK Shriver Center, Waltham, MA, USA.
CONTRACT NUMBER: DK38381 (NIDDK)
HD05515 (NICHD)
SOURCE: GENE THERAPY, (1996 May) 3 (5) 437-47.
Journal code: CCE. ISSN: 0969-7128.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY WEEK: 19970704
AB Recent reports have suggested that delivery of genes flanked by **AAV ITRs** may be useful for gene therapy of diseases that involve the brain. We have compared the efficiency of gene expression in vitro in CNS-derived cells from four different **promoters** when the **transgene** is flanked by **AAV ITRs**, using both transfection via cationic liposomes, and infection via **rAAV**. The human cytomegalovirus (CMV) immediate-early enhancer/**promoter**, the SV40 early enhancer/**promoter**, the JC polymovirus **promoter**, and the chicken beta-actin **promoter** coupled to the CMV enhancer were able to drive expression of the reporter gene beta-galactosidase in all tumor and primary brain cell cultures tested. Although the relative order of efficiency differed between cell types, the CMV **promoter** was always the strongest, generally by at least one order of magnitude. A comparison of the relative levels of expression seen between different cell types on transfection and infection suggest that not all CNS-derived cells are infected equally efficiently by **rAAVs**. High level of expression were seen within 24 h of **transgene** delivery by either transfection or infection, dropping dramatically within days. All cell types and

promoters showed the same decline, suggesting that transient expression by rep-**rAAVs** may be efficient, but stable expression as detected in this system is a low frequency event. In vivo studies using the CMV **promoter** also suggest that although rep-**rAAVs** are able to infect efficiently CNS cells and produce high levels of gene expression shortly after transduction, the majority of such infections do not lead to stable high-level expression of **transgenes**.

FILE 'CAPLUS' ENTERED AT 16:11:30 ON 01 DEC 2000
L24 2 S L10 AND INVERS? TERMIN? REPEAT
L25 0 S L24 NOT (L7 OR L14 OR L19)

FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 16:12:35 ON 01 DEC 2000
L26 4 S L24
L27 1 S L26 NOT (L8 OR L22)

L27 ANSWER 1 OF 1 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1999-562121 [47] WPIDS
CROSS REFERENCE: 2000-647078 [59]
DOC. NO. CPI: C1999-164000
TITLE: Production of helper-free recombinant **adeno -associated viruses**, useful for, e.g. production of transgene products in vitro.
DERWENT CLASS: B04 D16
INVENTOR(S): GAO, G; WILSON, J M
PATENT ASSIGNEE(S): (UYPE-N) UNIV PENNSYLVANIA
COUNTRY COUNT: 86
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9947691	A1	19990923	(199947)*	EN	53
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW					
AU 9930973	A	19991011	(200008)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9947691	A1	WO 1999-US5870	19990318
AU 9930973	A	AU 1999-30973	19990318

Searcher : Shears 308-4994

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9930973	A	Based on	WO 9947691

PRIORITY APPLN. INFO: US 1998-78908 19980320
AN 1999-562121 [47] WPIDS
CR 2000-647078 [59]
AB WO 9947691 A UPAB: 20001130
NOVELTY - Production of helper-free recombinant **adeno-associated viruses** using recombinant mammalian host cell is new.

DETAILED DESCRIPTION - (A) A novel mammalian host cell comprises:

(a) a transgene under the control of regulatory sequences directing expression and flanked by **adeno-associated virus** (**AAV**) **inverse terminal repeats**;

(b) an **AAV** rep sequence and an **AAV** cap sequence under the control of regulatory sequences directing expression; and

(c) DNA required to express an adenovirus E1a gene product, an adenovirus E1b gene product, and an adenovirus E2a gene product.

INDEPENDENT CLAIMS are also included for the following:

(1) producing recombinant **AAV** (**rAAV**) in the absence of contaminating helper virus or wild-type virus, comprising culturing a host cell as in (A);

(2) an **rAAV** produced by a method as in (1);

(3) a cell lysate comprising **rAAV** which is free of both wildtype **AAV** and helper adenovirus;

(4) a **rAAV** purified from a cell lysate as in (1), and

(5) an **rAAV** free of both wildtype (wt) **AAV** and helper adenovirus.

USE - The **rAAV** produced by the method may carry therapeutic transgenes or marker transgenes, and are particularly useful in transferring such transgenes to a host cell or tissue. These **rAAV** are useful in research reagents, as tools for the recombinant production of a transgene product in vitro, and as therapeutic reagents in gene therapy contexts.

ADVANTAGE - The methods enable the production of a **rAAV** without the need for a helper adenovirus, and without the problem of homologous recombination which produces contaminating re-assembled wt **AAV** during **rAAV** production. They simplify the production process for **rAAV** by eliminating the need for a purification step.

Dwg.0/3

(FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 16:13:52 ON 01 DEC 2000)

L28 1866 S GAO G?/AU — Author(s)
L29 31965 S WILSON J?/AU
L30 101 S L28 AND L29
L31 150 S (L30 OR L28 OR L29) AND L10
L32 22 S L31 AND ((INVERT? OR INVERS?)(W)TERMIN? REPEAT OR ITR)
L33 10 DUP REM L32 (12 DUPLICATES REMOVED)

L33 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 1
ACCESSION NUMBER: 2000:666895 CAPLUS
DOCUMENT NUMBER: 133:248054
TITLE: Compositions and methods for helper-free production of recombinant **adeno-associated viruses**
INVENTOR(S): **Gao, Guang-ping; Wilson, James M.**
PATENT ASSIGNEE(S): The Trustees of the University of Pennsylvania, USA
SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000055342	A1	20000921	WO 2000-US4755	20000224
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
WO 9947691	A1	19990923	WO 1999-US5870	19990318
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN. INFO.: WO 1999-US5870 19990318

Searcher : Shears 308-4994

US 1999-404555 19990923
US 1998-78908 19980320

AB A method for producing recombinant **adeno-assocd. virus** in the absence of contaminating helper virus or wild-type virus involves culturing a mammalian host cell contg. a transgene flanked by **adeno-assocd. virus** (**AAV**) **inverse terminal repeats** and under the control of regulatory sequences directing expression thereof, an **AAV** rep sequence and an **AAV** cap sequence under the control of regulatory sequences directing expression thereof; and the min. adenovirus DNA required to express an E1a gene product, an E1b gene product and an E2a gene product, and isolating therefrom a recombinant **AAV** which expresses the transgene in the absence of contaminating helper virus or wild-type **AAV**. This method obviates a subsequent purifn. step to purify **rAAV** from contaminating virus. Also provided are various embodiments of the host cell. The invention is based on the discovery that only the adenovirus E1 and E2a genes are necessary for prodn. of recombinant **AAV**. Wild-type **AAV** are not produced because the adenoviral proteins necessary for homologous recombination are not present.

REFERENCE COUNT: 9
REFERENCE(S):
(1) Avigen Inc; WO 9717458 A 1997
(2) Cell Genesys Inc; WO 9614061 A 1996
(3) Coovert, D; CURRENT OPINION IN NEUROLOGY 1994, V7(5), P463 MEDLINE
(4) Gao, G; HUMAN GENE THERAPY 1998, V9(16), P2353 CAPLUS
(6) Shenk, T; US 5436146 A 1995 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 2
ACCESSION NUMBER: 2000:335582 CAPLUS
DOCUMENT NUMBER: 133:1504
TITLE: **Adeno-associated virus** serotype 1 nucleic acid and protein sequences and their use as gene therapy vectors in host cells
INVENTOR(S): **Wilson, James M.**; Xiao, Weidong
PATENT ASSIGNEE(S): The Trustees of the University of Pennsylvania, USA
SOURCE: PCT Int. Appl., 108 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2000028061	A2	20000518	WO 1999-US25694	19991102
WO 2000028061	A3	20000803		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1998-107114 19981105

AB The nucleic acid sequences of **adeno-assocd. virus** (**AAV**) serotype 1 are provided, as are vectors and host cells contg. these sequences and functional fragments thereof. The entire **AAV**-1 genome is 4718 nucleotides in length, within the range of other known serotypes. Amon particularable desirable **AAV**-1 fragments are the **inverted terminal repeat** sequences (**ITRs**), rep genes, and capsid genes. Also provided are methods of delivering genes via **AAV**-1 derived vectors. Cassettes may contain the **AAV**-1 **ITRs** of the invention flanking a selected transgene, or the rep and/or cap proteins for use in producing recombinant virus. Exemplary transducing vectors based on **AAV**-1 capsid proteins and conting. genes encoding human .alpha.1-antitrypsin or murine erythropoietin under control of a cytomegalovirus-enhanced .beta.-actin promoter are tested both in vivo and in vitro.

L33 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 3
ACCESSION NUMBER: 1999:614159 CAPLUS
DOCUMENT NUMBER: 131:224468
TITLE: Cells and methods for helper-free production of recombinant **adeno-associated viruses**
INVENTOR(S): **Gao, Guang-Ping; Wilson, James M.**
PATENT ASSIGNEE(S): Trustees of the University of Pennsylvania, USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9947691	A1	19990923	WO 1999-US5870	19990318

Searcher : Shears 308-4994

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9930973 A1 19991011 AU 1999-30973 19990318
WO 2000055342 A1 20000921 WO 2000-US4755 20000224
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1998-78908 19980320
WO 1999-US5870 19990318
US 1999-404555 19990923

AB A method for producing recombinant **adeno-assocd. virus** in the absence of contaminating helper virus or wild-type virus involves culturing a mammalian host cell contg. a transgene flanked by **adeno-assocd. virus (AAV) inverse terminal repeats** and under the control of regulatory sequences directing expression thereof, an **AAV** rep sequence and an **AAV** cap sequence under the control of regulatory sequences directing expression thereof; and the min. adenovirus DNA required to express an E1a gene product, an E1b gene product and an E2a gene product, and isolating therefrom a recombinant **AAV** which expresses the transgene in the absence of contaminating helper virus or wildtype **AAV**. This method obviates a subsequent purifn. step to purify **rAAV** from contaminating virus. Also provided are various embodiments of the host cell. The invention is based on the discovery that only the adenovirus E1 and E2a genes are necessary for prodn. of recombinant **AAV**. Wild-type **AAV** are not produced because the adenoviral proteins necessary for homologous recombination are not present.

REFERENCE COUNT: 9
REFERENCE(S): (1) Avigen Inc; WO 9717458 A 1997
(2) Cell Genesys Inc; WO 9614061 A 1996
(3) Coovert, D; Current Opinion in Neurology 1994, V7(5), P463 MEDLINE
(4) Gao, G; Human Gene Therapy 1998, V9(16), P2353 CAPLUS

Searcher : Shears 308-4994

(6) Shenk, T; US 5436146 A 1995 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 4
ACCESSION NUMBER: 1999:223068 CAPLUS
DOCUMENT NUMBER: 130:247865
TITLE: Manufacture of recombinant **adeno-associated viruses** in high titer using producer cells carrying integrated rep and cap genes
INVENTOR(S): **Wilson, James M.; Gao, Guang-Ping**
PATENT ASSIGNEE(S): The Trustees of the University of Pennsylvania, USA
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9915685	A1	19990401	WO 1998-US19463	19980918
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9893970	A1	19990412	AU 1998-93970	19980918
EP 1015619	A1	20000705	EP 1998-947114	19980918
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRIORITY APPLN. INFO.:			US 1997-59340	19970919
			WO 1998-US19463	19980918

AB Methods for efficient prodn. of recombinant **adeno-assocd. virus** (**AAV**) using a host cell carrying the **AAV** rep and cap genes stably integrated into the cell's chromosomes are described. The integrated rep and cap genes are under the control of promoters that are induced by a specific stimulus such as infection of the cell with a helper virus, or introduction of a helper gene or helper gene product. Preferably, the rep and cap genes are integrated in tandem repeat arrays under control of the **AAv** p5 promoter. Cells in which the genes have been induced are then superinfected with a

virus or plasmid vector contg. adenovirus cis-elements necessary for replication and virion encapsidation, **AAV** sequences comprising the 5' and 3' **ITRs**, and a selected gene operatively linked to regulatory sequences directing its expression, which is flanked by the above-mentioned **AAV** sequences. The vector to be packaged does not carry the rep and cap genes. The resulting **AAV** is essentially free of replication competent virus and yields of virus of .gtoreq.103 per cell are obtained. A novel B50 producer cell line is described. **AAV** carrying a monkey erythropoietin gene constructed using this method were injected into immune-deficient or immune-competent mice. Virus manufd. with B50 cells was more infective than that manufd. with the prior art 293 cell system. The mice had .apprx.4-fold higher levels of erythropoietin and a significantly higher hematocrit than control cells. Cells manufd.

REFERENCE COUNT: 8

REFERENCE(S):
(1) Allen, J; WO 9617947 A 1996
(3) Clark, K; Gene Therapy 1996, V3, P1124 CAPLUS
(4) Clark, K; Human Gene Therapy 1995, V6(10), P1329 CAPLUS
(5) Flotte, T; Gene Therapy 1995, V2(1), P29 CAPLUS
(7) Tamayose, K; Human Gene Therapy 1996, V7(4), P507 MEDLINE
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 5

ACCESSION NUMBER: 1999:220078 CAPLUS

DOCUMENT NUMBER: 130:233247

TITLE: Expression vectors and host cells for the manufacture of **adeno-associated viruses** carrying foreign DNA

INVENTOR(S): **Wilson, James M.**; Xiao, Weidong

PATENT ASSIGNEE(S): The Trustees of the University of the Pennsylvania, USA

SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9914354	A1	19990325	WO 1998-US19479	19980918

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP,

KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9893191 A1 19990405 AU 1998-93191 19980918
PRIORITY APPLN. INFO.: US 1997-59330 19970919
WO 1998-US19479 19980918

AB Host cells and expression vectors that can be used to manuf. **adeno-assocd. virus** carrying cloned genes in high titer are described. This is achieved by limiting the expression of the rep68 and rep78 genes without affecting the expression of the rep40 and rep52 and structural protein genes. An expression vector for the rep and cap genes uses the parvovirus P5 promoter to drive expression. The promoter is sepd. from the genes by a spacer that limits expression of the rep68 and rep78 genes. There are no particular sequence requirements for the spacer. A second vector carries a minigene of interest flanked by a pair of **AAV inverted terminal repeats**. Expts. detg. the lengths of spacer that give the greatest yield of virus are reported. A spacer of .ltoreq.500 base pairs gave the highest titer of virus although increased titers could be found with spacers of up to 3.8 kb.

REFERENCE COUNT: 6
REFERENCE(S):
(1) Allen, J; WO 9617947 A 1996
(2) Avigen Inc; WO 9706272 A 1997
(3) Graham, F; WO 9640955 A 1996
(4) Pennsylvania, U; WO 9810086 A 1998
(5) Sambrook, J; Molecular Cloning A laboratory manual 1989
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:125734 CAPLUS
DOCUMENT NUMBER: 130:178345
TITLE: Hybrid adenovirus-**adeno-associated virus** and its use in cell transformation
INVENTOR(S): **Wilson, James M.**; Kelley, William M.; Fisher, Krishna J.
PATENT ASSIGNEE(S): The Trustees of the University of Pennsylvania, USA
SOURCE: U.S., 45 pp., Cont.-in-part of U.S. Ser. No. 331,384.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5871982	A	19990216	US 1997-836087	19970825
US 5856152	A	19990105	US 1994-331384	19941028
WO 9613598	A2	19960509	WO 1995-US14018	19951027
WO 9613598	A3	19960815		

W: AL, AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN

RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

EP 1046711	A2	20001025	EP 2000-103600	19951027

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE

PRIORITY APPLN. INFO.:	US 1994-331384	19941028
	WO 1995-US14018	19951027
	EP 1995-942840	19951027

AB The present invention provides a hybrid vector construct which comprises a portion of an adenovirus, 5' and 3' **inverted terminal repeat** (**ITR**) sequences from an **adeno-assocd. virus** (**AAV**), and a selected transgene. Also provided is a hybrid virus linked via a polycation conjugate to an **AAV** rep gene to form a single particle. These trans-infection particles are characterized by high titer transgene delivery to a host cell and the ability to stably integrate the transgene into the host cell chromosome. Also disclosed is the use of the hybrid vectors and viruses to produce large quantities of recombinant **AAV**. Hybrid adeno-**adeno-assocd. virus** Ad.AV.CMVLacZ was prepd. as well as a complex of polylysine with this hybrid virus and plasmid pRep78/52 (providing the **adeno-assocd. virus** rep gene). HeLa cells were infected with the complex and the lacZ gene was found to be integrated into the cell genome.

REFERENCE COUNT: 46
REFERENCE(S):
(1) Anon; WO 9118088 1991 CAPLUS
(2) Anon; WO 9324641 1993 CAPLUS
(3) Anon; WO 9412649 1994 CAPLUS
(4) Anon; WO 9413788 1994 CAPLUS
(5) Anon; WO 9417832 1994 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 6
ACCESSION NUMBER: 1999:263448 CAPLUS
DOCUMENT NUMBER: 131:67660

TITLE: Gene therapy vectors based on **adeno-associated virus** type 1

AUTHOR(S): Xiao, Weidong; Chirmule, Narendra; Berta, Scott C.; McCullough, Beth; **Gao, Guangping**; **Wilson, James M.**

CORPORATE SOURCE: Institute for Human Gene Therapy and Departments of Molecular and Cellular Engineering and of Medicine, University of Pennsylvania, Philadelphia, PA, 19104, USA

SOURCE: J. Virol. (1999), 73(5), 3994-4003
CODEN: JOVIAM; ISSN: 0022-538X

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The complete sequence of **adeno-assocd. virus** type 1 (**AAV**-1) was defined. Its genome of 4,718 nucleotides demonstrates high homol. with those of other **AAV** serotypes, including **AAV**-6, which appears to have arisen from homologous recombination between **AAV**-1 and **AAV**-2. Anal. of sera from nonhuman and human primates for neutralizing antibodies (NAB) against **AAV**-1 and **AAV**-2 revealed the following. (i) NAB to **AAV**-1 are more common than NAB to **AAV**-2 in nonhuman primates, while the reverse is true in humans; and (ii) sera from 36% of nonhuman primates neutralized **AAV**-1 but not **AAV**-2, while sera from 8% of humans neutralized **AAV**-2 but not **AAV**-1. An infectious clone of **AAV**-1 was isolated from a replicated monomer form, and vectors were created with **AAV**-2 **inverted terminal repeats** and **AAV**-1 Rep and Cap functions. Both **AAV**-1- and **AAV**-2-based vectors transduced murine liver and muscle in vivo; **AAV**-1 was more efficient for muscle, while **AAV**-2 transduced liver more efficiently. Strong NAB responses were detected for each vector administered to murine skeletal muscle; these responses prevented readministration of the same serotype but did not substantially cross-neutralize the other serotype. Similar results were obsd. in the context of liver-directed gene transfer, except for a significant, but incomplete, neutralization of **AAV**-1 from a previous treatment with **AAV**-2. Vectors based on **AAV**-1 may be preferred in some applications of human gene therapy.

REFERENCE COUNT: 34

REFERENCE(S):
(1) Balague, C; J Virol 1997, V71, P3299 CAPLUS
(4) Chiorini, J; J Virol 1997, V71, P6823 CAPLUS
(5) Clark, K; Gene Ther 1996, V3, P1124 CAPLUS
(6) Clark, K; Hum Gene Ther 1995, V6, P1329 CAPLUS
(7) Fisher, K; J Virol 1996, V70, P520 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 7
ACCESSION NUMBER: 1998:176036 CAPLUS
DOCUMENT NUMBER: 128:214186
TITLE: Regulated control of **adeno-associated virus** replication using bacteriophage T7 promoters and regulated expression of the T7 polymerase gene
INVENTOR(S): **Wilson, James M.**; Chen, Nancie
PATENT ASSIGNEE(S): Trustees of the University of Pennsylvania, USA; Wilson, James M.; Chen, Nancie
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9810088	A1	19980312	WO 1997-US15716	19970904
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9741833	A1	19980326	AU 1997-41833	19970904
AU 722624	B2	20000810		
EP 931158	A1	19990728	EP 1997-939829	19970904
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRIORITY APPLN. INFO.:			US 1996-24699	19960906
			WO 1997-US15716	19970904

AB A method for efficient replication and packaging of **adeno-assocd. virus** vectors carrying foreign genes for use in gene therapy is described. The method avoids the toxicity problems assocd. with high levels of the rep gene product. The method uses three sep. expression constructs. One of these carries an expression cassette for the T7 polymerase gene. The preferred promoter is the cytomegalovirus immediate-early promoter. A second carries the virus rep and cap genes under the control of T7 promoters. A third vector contains a cassette in which the **adeno-assocd. virus inverted terminal repeats** flank a minigene. Quiescent host cells carrying one or two of these vectors can be prepd. with

introduction of the third vector inducing formation of virus.

L33 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 8
ACCESSION NUMBER: 1998:176034 CAPLUS
DOCUMENT NUMBER: 128:214185
TITLE: Use of the cre-loxP system to control expression of genes in the manufacture of adenovirus vectors for gene therapy
INVENTOR(S): **Wilson, James M.**; Phaneuf, Daniel
PATENT ASSIGNEE(S): Trustees of the University of Pennsylvania, USA; Wilson, James M.; Phaneuf, Daniel
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9810086	A1	19980312	WO 1997-US15691	19970904
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9741830	A1	19980326	AU 1997-41830	19970904
AU 722375	B2	20000803		
EP 950111	A1	19991020	EP 1997-939821	19970904
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRIORITY APPLN. INFO.:			US 1996-25323	19960906
			WO 1997-US15691	19970904

AB A method for the manuf. of **adeno-assocd. virus** carrying a foreign gene in which the cre-loxP system is used to regulate expression of the rep/cap genes is described. Regulated expression of these genes allows efficient packaging of a gene flanked by **adeno-assocd. virus inverted terminal repeats** without a build up of toxic levels of the rep gene product. The method uses three vectors. A first vector is an expression vector for the cre gene, the second is an expression vector for the rep/cap genes in which the promoter is sepd. from the coding region by an insert flanked by loxP sites and rep/cap, and a third vector contains a minigene contg. a transgene and regulatory sequences flanked by

AAV ITRs. The third vector contains an expression cassette for the therapeutic gene flanked by **AAV inverted terminal repeats**. The host cell stably or inducibly expresses the cre gene and two vectors carrying the other elements of the system are introduced into the host cell.

L33 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 9
ACCESSION NUMBER: 1996:428562 CAPLUS
DOCUMENT NUMBER: 125:78506
TITLE: Hybrid adenovirus-**adeno-associated virus** and its use in cell transformation
INVENTOR(S): **Wilson, James M.**; Kelley, William M.; Fisher, Krishna J.
PATENT ASSIGNEE(S): Trustees of the University of Pennsylvania, USA
SOURCE: PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9613598	A2	19960509	WO 1995-US14018	19951027
WO 9613598	A3	19960815		
W: AL, AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5856152	A	19990105	US 1994-331384	19941028
CA 2203808	AA	19960509	CA 1995-2203808	19951027
AU 9644055	A1	19960523	AU 1996-44055	19951027
AU 695811	B2	19980820		
EP 797678	A2	19971001	EP 1995-942840	19951027
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV				
JP 10507928	T2	19980804	JP 1995-514801	19951027
EP 1046711	A2	20001025	EP 2000-103600	19951027
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
US 5871982	A	19990216	US 1997-836087	19970825
PRIORITY APPLN. INFO.:			US 1994-331384	19941028
			EP 1995-942840	19951027
			WO 1995-US14018	19951027

Searcher : Shears 308-4994

AB The present invention provides a hybrid vector construct which comprises a portion of an adenovirus, 5' and ' **ITR** sequences from an **AAV**, and a selected transgene. Also provided is a hybrid virus linked via a polycation conjugate to an **AAV** rep gene to form a single particle. These trans-infection particles are characterized by high titer transgene delivery to a host cell and the ability to stably integrate the transgene into the host cell chromosome. Also disclosed is the use of the hybrid vectors and viruses to produce large quantities of recombinant **AAV**. Hybrid adeno-**adeno-assocd. virus** Ad.AV.CMVLacZ was prepd. as well as a complex of polylysine with this hybrid virus and plasmid pRep78/52 (providing the **adeno-assocd. virus** rep gene). HeLa cells were infected with the complex and the lacZ gene was found to be integrated into the cell genome.

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